IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	**Confirmation No. 9103**
Tsuneo YASUMA et al.	:	Attorney Docket No. 2006_0878A
Serial No. 10/584,481	:	Group Art Unit 1625
Filed June 23, 2006	:	Examiner Taofiq A. Solola
3-(4-BENZYLOXYPHENYL)PROPANOIC ACID DERIVATIVES	:	**Mail Stop: AF**

SUBMISSION OF VERIFIED ENGLISH TRANSLATION

OF FIRST PRIORITY DOCUMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Enclosed herewith is a verified English translation of JP 2003-431629.

Please make this a permanent part of the application file.

Respectfully submitted,

Tsuneo YASUMA et al.

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IN RE APPLICATION OF:
Tsuneo YASUMA et al.
SERIAL NO.: 10/584,481 : GROUP ART UNIT: 1625
FILED: June 23, 2006 : EXAMINER: Taofiq A. Solola
FOR: 3-(4-BENZYLOXYPHENYL)PROPANOIC ACID DERIVATIVES

TRANSLATOR'S DECLARATION

Honorable Commissioner for Patents
P.O.Box 1450
Alexandria, Virginia 22313-1450

Sir:

I, Ritsuko Arimura, declare:

That I am well acquainted with both the Japanese and English languages;

That the attached document represents a true English translation of Japanese Patent Application No. 2003-431629 filed on December 25, 2003; and

That I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 16th day of July, 2008.

Ritsuko Arimura

(Translation)

J A P A N P A T E N T O F F I C E

This is to certify that the annexed is a true copy of the following application as filed with this Office.

Date of Application : December 25, 2003

Application Number : 431629/2003

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is JP2003-431629

Applicant(s) : Takeda Pharmaceutical Company Limited

January 25, 2005

Commissioner, Japan Patent Office
Hiroshi Ogawa

【Document】 Petition for Patent
【Reference Number】 A6181
【Submission Date】 December 25, 2003
【To】 Commissioner of the Patent Office
【International Classification】 C07C 53/122
C07C 69/102
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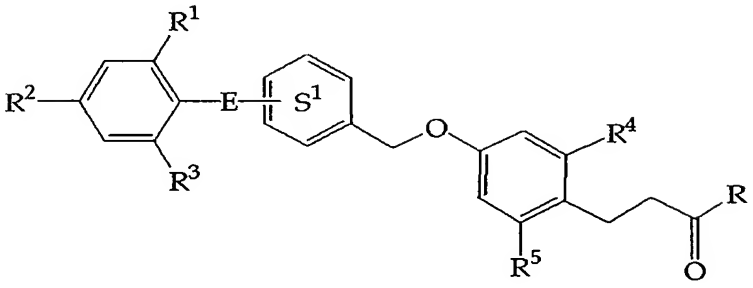
【Official Fee】
【Deposit Ledger Number】 006965
【Payment Amount】 ¥21,000
【List of the Annexed Documents】
【Document】 Claims One copy
【Document】 Specification One copy
【Document】 Abstract One copy
【Number of General Power of Attorney】 0109317

【Document】 Claims

【Claim 1】 A compound represented by the formula (I):



(I)

wherein

R^1, R^3, R^4 and R^5

are the same or different and each is a hydrogen atom, a halogen atom, an optionally substituted hydrocarbon group or an optionally substituted hydroxy group, R^2 is a halogen atom, an optionally substituted hydrocarbon group, an optionally substituted hydroxy group, an optionally substituted amino group, an optionally substituted mercapto group or an optionally substituted heterocyclic group,

E is a bond, an optionally substituted C_{1-4} alkylene group, $-W^1-O-W^2-$, $-W^1-S-W^2-$ or $-W^1-N(R^6)-W^2-$ (wherein W^1 and W^2 are the same or different and each is a bond or an optionally substituted C_{1-3} alkylene group, and R^6 is a hydrogen atom, an optionally substituted acyl group or an optionally substituted hydrocarbon group),

ring S^1 is a benzene ring optionally further having substituent(s) selected from a halogen atom, an optionally substituted hydrocarbon group, an optionally substituted hydroxy group and an optionally substituted amino group; and

R is an optionally substituted hydroxy group or an optionally substituted amino group;

provided that R^1 and R^3 are not simultaneously a hydrogen atom, or a salt thereof.

【Claim 2】 A prodrug of a compound of claim 1 or a salt thereof.

[Claim 3] The compound of claim 1, wherein R^4 and R^5 are the same or different and each is a hydrogen atom or a halogen atom, or a salt thereof.

[Claim 4] The compound of claim 1, wherein E is a bond, or a salt thereof.

[Claim 5] The compound of claim 1, wherein R is a hydroxy group, or a salt thereof.

[Claim 6] A GPR40 receptor function modulator comprising a compound of claim 1 or a salt thereof or a prodrug thereof.

[Claim 7] A pharmaceutical agent comprising a compound of claim 1 or a salt thereof or a prodrug thereof.

[Claim 8] The pharmaceutical agent of claim 7, which is an agent for the treatment of diabetes.

【Document】 Specification

【Title of the Invention】 3-(4-BENZYLOXYPHENYL)PROPANOIC ACID DERIVATIVES

【Technical Field of the Invention】

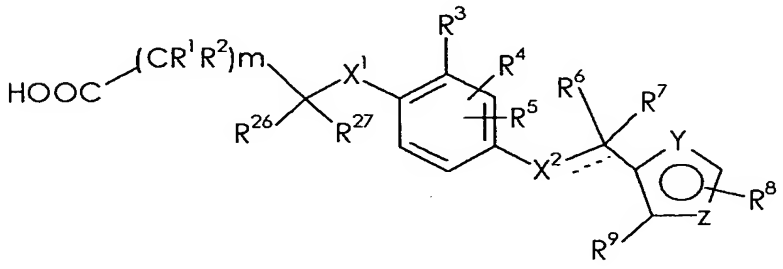
The present invention relates to a novel compound having GPR40 receptor function modifying action and which is useful as an agent for the prophylaxis or treatment of diabetes.

【Background Art】

It has been reported in recent years that a ligand of GPR40, which is one of the G Protein-Coupled Receptors (GPCR), is fatty acid and GPR40 in pancreatic β cell is deeply involved in insulin secretion action (non-patent reference 1). Thus, a GPR40 agonist promotes insulin secretion, a GPR40 antagonist inhibits insulin secretion, and the agonist and the antagonist are useful as an agent for the prophylaxis or treatment of type 2 diabetes, obesity, impaired glucose tolerance, insulin resistance, neurodegenerative diseases (Alzheimer's disease) and the like (patent references 1 and 2).

On the other hand, many compounds useful as an agent for the prophylaxis or treatment of diabetes have been reported.

For example, patent reference 3 discloses that a peroxisome proliferator activated receptor (PPAR) modulator represented by the formula:

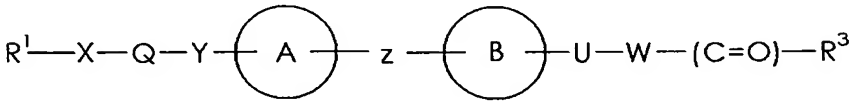


wherein X^1: a C_{1-3} alkyl and the like; R^1, R^2: H and the like; R^3, R^4, R^5: H, CH_3 and the like; R^{26}, R^{27}: H and the like; m: 0-3; X^2: O and the like; R^6, R^7: H and the like; Y, Z: one is CH and the

other is S or O; R^8: a phenyl and the like; R^9: a C_{1-6} alkyl and the like,

is useful as an agent for the prophylaxis or treatment of PPAR mediated disease (e.g., diabetes).

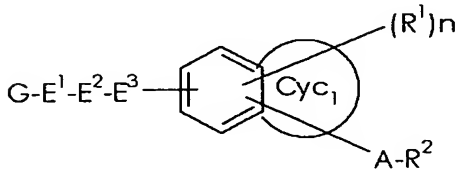
Patent reference 4 discloses that an alkanoic acid derivative represented by the formula:



wherein R^1: an optionally substituted 5-membered aromatic heterocyclic group; X: a bond, O, S, $-NR^6-$ (R^6: H, an optionally substituted hydrocarbon group and the like) and the like; Q: a divalent C_{1-20} hydrocarbon group; Y: a bond, O, S, $-NR^7-$ (R^7: H, an optionally substituted hydrocarbon group and the like) and the like; ring A: an aromatic ring optionally further having 1 to 3 substituent(s); Z: $-(CH_2)n-Z^1-$ (n: 1-8, Z^1: O and the like) and the like; ring B: a benzene ring optionally further having 1 to 3 substituent(s) and the like; U: a bond and the like; W: a divalent C_{1-20} hydrocarbon group; R^3: $-OR^8-$ (R^8: H, an optionally substituted hydrocarbon group) or $-NR^9R^{10}-$ (R^9, R^{10}: H, an optionally substituted hydrocarbon group and the like) and the like; provided that when ring B is a benzene ring optionally further having 1 to 3 substituent(s), then U is a bond,

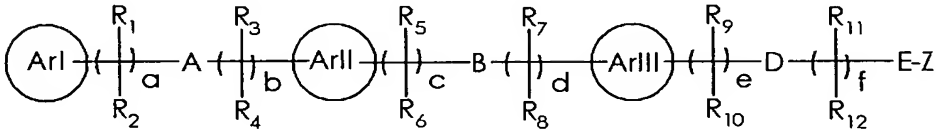
is useful as an agent for the prophylaxis or treatment of diabetes, hyperlipidemia, impaired glucose tolerance and the like.

Patent reference 5 discloses that a compound represented by the formula:



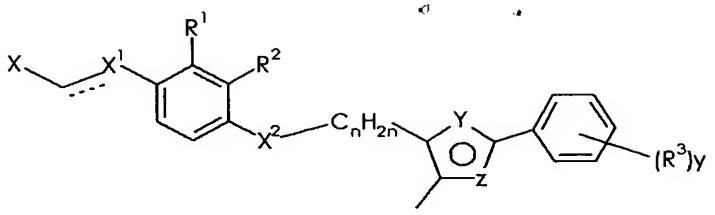
wherein R^1: a C_{1-8} alkyl, a C_{1-8} alkoxy, a halogen atom, a trifluoromethyl and the like; R^2: $-COOR^3$ (R^3: H, a C_{1-4} alkyl) and the like; A: a C_{1-8} alkylene and the like; G: a carbon ring optionally substituted by a C_{1-8} alkyl, a C_{1-8} alkoxy, a halogen atom, a trifluoromethyl or a nitro, and the like; E^1: a C_{1-8} alkylene and the like; E^2 : -O- and the like; E^3: a single bond and the like; n: 0, 1; Cycl ring: absent and the like, has a PPAR receptor regulating action, and is useful as an agent for the prophylaxis or treatment of metabolism abnormality diseases such as diabetes, obesity, syndrome X, hypercholesterolemia, hyperlipoproteinemia and the like, and the like.

Patent reference 6 discloses that a compound represented by the formula:



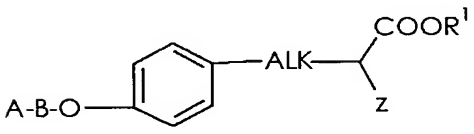
wherein ring ArI, ring ArII, ring ArIII: an optionally substituted aryl and the like; A: -O-, -S-, a bond, $-NR_{13}-$ (R_{13}: H, an alkyl and the like) and the like; B: -O- and the like; D: a bond, an ethylene; E: a bond, an ethylene; X: H and the like, Z: $R_{21}O_2C-$, $(R_{21})_2NCO-$ (R_{21}: H, an alkyl and the like) and the like; a, b, c, e: 0-4; d: 0-5; f: 0-6; R_1-R_{12}: H and the like, is useful as a PPAR ligand receptor binder, PPAR receptor agonist or PPAR receptor antagonist, and can be used as an agent for the treatment of diabetes.

Patent reference 7 discloses that a compound represented by the formula:



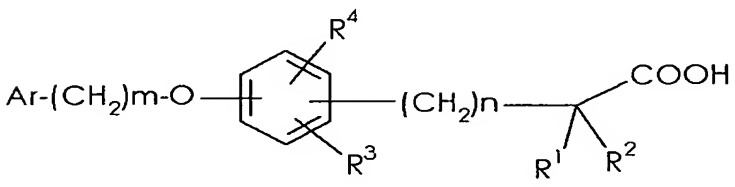
wherein X: COOH (containing ester) and the like; X^1: CH_2 etc.; dotted line shows double bond only when X^1 is CH; X^2: O and the like; R^1, R^2: H, Me and the like; n: 1, 2; Y, Z: one is N and the other is S or O; y: an integer of 0-5; R^3: CF_3 and the like, can be used as a PPARδ agonist, and is useful as an agent for the prophylaxis or treatment of PPARδ mediated disease (e.g., hyperlipidemia, arteriosclerosis, type I or II diabetes and the like).

Patent reference 8 discloses that a compound represented by the formula:



wherein A: a phenyl optionally substituted a halogen and the like, and the like; B: a C_{1-6} alkylene and the like; ALK: a C_{1-3} alkylene; R^1: H, a C_{1-3} alkyl; Z: -(C_{1-3} alkylene)phenyl optionally substituted by a halogen and the like,
is useful as a PPARγ agonist, can be used as an agent for the prophylaxis or treatment of hyperglycemia, type I or II diabetes, hyperlipidemia and the like.

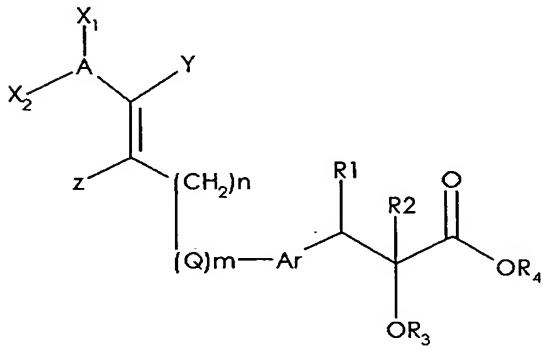
Patent reference 9 discloses that a compound represented by the formula:



wherein Ar: a phenyl substituted by 1 to 5 the same or different halogen atom(s) and the like, and the like; R^1: a halogen atom and the like; R^2: H and the like; R^3, R^4: H, a halogen atom; m: 1, 2; n: 2-7,

has a superior insulin sensitizing action, hypoglycemic action, hypolipidemic action, antiinflammatory action, immunomodulating action, lipoperoxide production suppressive action and PPAR activating action, and is useful as an agent for the treatment of diabetes.

Patent reference 10 discloses that a compound represented by the formula:



wherein A: an aryl optionally substituted by OH and the like; X^1, X^2: H and the like; Y, Z: H and the like; n: 0-3; m: 0, 1; Q: O and the like; Ar: an arylene and the like; R^1-R^4: H and the like, is useful as an agent for the treatment of PPAR related diseases, and useful as an agent for the treatment of, for example, type 2 diabetes, impaired glucose tolerance, insulin resistance, hypertriglyceridemia and the like.

However, it has not been disclosed at all that these known therapeutic drugs for diabetes have a GPR40 receptor function modifying action, and there is no report on a compound having a GPR40 receptor function modifying action (compound useful as a GPR40 agonist or GPR40 antagonist). Under the circumstances, development of a compound having a GPR40 receptor function modifying action has been desired.

【Non-patent Reference 1】 Nature, 2003, vol. 422, pages 173-176

【Patent Reference 1】 WO03/068959

【Patent Reference 2】 WO02/057783

【Patent Reference 3】 WO02/092590

【Patent Reference 4】 WO02/053547

【Patent Reference 5】 WO99/11255

【Patent Reference 6】 WO00/64876

【Patent Reference 7】 WO01/00603

【Patent Reference 8】 WO97/31907

【Patent Reference 9】 WO02/083616

【Patent Reference 10】 WO01/55085

【Disclosure of the Invention】

【Problems to be Solved by the Invention】

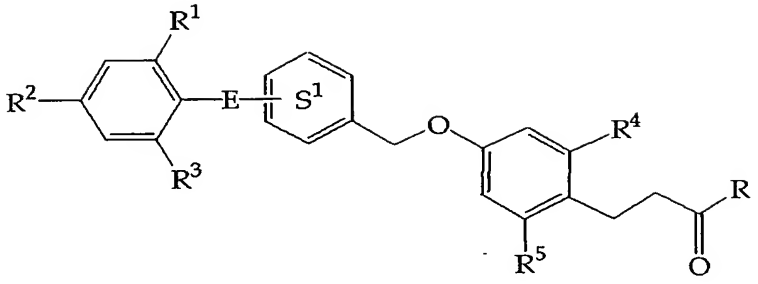
The present invention aims at providing a novel compound having a GPR40 receptor function modifying action, which is useful as an insulin secretagogue or an agent for the prophylaxis or treatment of diabetes and the like.

【Means of Solving the Problems】

The present inventors have intensively conducted various studies and found that the compound represented by the following formula (I) unexpectedly has a superior GPR40 receptor agonist activity, shows superior properties as a pharmaceutical product such as stability and the like, and can be a safe and useful pharmaceutical agent for the prophylaxis or treatment of GPR40 receptor related disease state or diseases in mammal, and completed the present invention.

Accordingly, the present invention provides the following.

(1) A compound represented by the formula:



(I)

wherein

R^1, R^3, R^4 and R^5

are the same or different and each is a hydrogen atom, a halogen atom, an optionally substituted hydrocarbon group or an optionally substituted hydroxy group; R^2 is a halogen atom, an optionally substituted hydrocarbon group, an optionally substituted hydroxy group, an optionally substituted amino group, an optionally substituted mercapto group or an optionally substituted heterocyclic group;

E is a bond, an optionally substituted C_{1-4} alkylene group, $-W^1-O-W^2-$, $-W^1-S-W^2-$ or $-W^1-N(R^6)-W^2-$ (wherein W^1 and W^2 are the same or different and each is a bond or an optionally substituted C_{1-3} alkylene group, and R^6 is a hydrogen atom, an optionally substituted acyl group or an optionally substituted hydrocarbon group);

ring S^1 is a benzene ring optionally further having substituent(s) selected from a halogen atom, an optionally substituted hydrocarbon group, an optionally substituted hydroxy group and an optionally substituted amino group; and

R is an optionally substituted hydroxy group or an optionally substituted amino group;

provided that R^1 and R^3 are not simultaneously a hydrogen atom, or a salt thereof.

(2) A prodrug of a compound of (1) above or a salt thereof.

(3) The compound of (1) above, wherein R^4 and R^5 are the same or different and each is a hydrogen atom or a halogen atom, or a salt thereof.

(4) The compound of (1) above, wherein E is a bond, or a salt thereof.

(5) The compound of (1) above, wherein R is a hydroxy group, or a salt thereof.

(6) A GPR40 receptor function modulator comprising a compound of (1) above or a salt thereof or a prodrug thereof.

(7) A pharmaceutical agent comprising a compound of (1) above or a salt thereof or a prodrug thereof.

(8) The pharmaceutical agent of (7) above, which is an agent for the treatment of diabetes.

【Effect of the Invention】

The compound of the present invention has a superior GPR40 receptor function modifying action, and can be used as an agent for the prophylaxis or treatment of diabetes and the like.

【Best Mode for Carrying out the Invention】

Unless otherwise specified, as the "halogen atom" in the present specification, fluorine atom, chlorine atom, bromine atom, iodine atom can be mentioned.

Unless otherwise specified, as the "optionally substituted hydrocarbon group" in the present specification, for example, "optionally substituted C_{1-6} alkyl group", "optionally substituted C_{2-6} alkenyl group", "optionally substituted C_{2-6} alkynyl group", "optionally substituted C_{3-8} cycloalkyl group", "optionally substituted C_{6-14} aryl group", "optionally substituted C_{7-16} aralkyl group" and the like can be mentioned.

Unless otherwise specified, as the "C_{1-6} alkyl group" in the present specification, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl and the like can be mentioned.

Unless otherwise specified, as the "C_{2-6} alkenyl group" in the present specification, for example, vinyl, propenyl, isopropenyl, 2-buten-1-yl, 4-penten-1-yl, 5-hexen-1-yl and the like can be mentioned.

Unless otherwise specified, as the "C_{2-6} alkynyl group" in the present specification, for example, 2-butyn-1-yl, 4-pentyn-1-yl, 5-hexyn-1-yl and the like can be mentioned.

Unless otherwise specified, as the "C_{3-8} cycloalkyl group" in the present specification, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like can be mentioned.

Unless otherwise specified, as the "C_{6-14} aryl group" in the present specification, for example, phenyl, 1-naphthyl, 2-naphthyl, 2-biphenylyl, 3-biphenylyl, 4-biphenylyl, 2-anthryl and the like can be mentioned. The C_{6-14} aryl may be optionally saturated partially, and as the partially saturated C_{6-14} aryl, for example, tetrahydronaphthyl and the like can be mentioned.

Unless otherwise specified, as the "C_{7-16} aralkyl group" in the present specification, for example, benzyl, phenethyl, diphenylmethyl, 1-naphthylmethyl, 2-naphthylmethyl, 2,2-diphenylethyl, 3-phenylpropyl, 4-phenylbutyl, 5-phenylpentyl, 2-biphenylylmethyl, 3-biphenylylmethyl, 4-biphenylylmethyl and the like can be mentioned.

Unless otherwise specified, as the "optionally substituted hydroxy group" in the present specification, for example, "hydroxy group", "optionally substituted C_{1-10} alkoxy group", "optionally substituted heterocyclyloxy group", "optionally substituted C_{6-14} aryloxy group", "optionally substituted C_{7-16} aralkyloxy group" and the like can be mentioned.

Unless otherwise specified, as the "C_{1-6} alkoxy group" in the present specification, for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy, hexyloxy and the like can be mentioned. As the "C_{1-10} alkoxy group" in the present specification, heptyloxy, octyloxy, nonyloxy, decyloxy and the like can be mentioned besides the above-mentioned C_{1-6} alkoxy group.

As the "heterocyclyloxy group" in the present specification, hydroxy group substituted by a "heterocyclic

group" below can be mentioned. As preferable examples of the heterocyclyloxy group, tetrahydropyranyloxy, thiazolyloxy, pyridyloxy, pyrazolyloxy, oxazolyloxy, thienyloxy, furyloxy and the like can be mentioned.

Unless otherwise specified, as the "C_{6-14} aryloxy group" in the present specification, for example, phenoxy, 1-naphthyloxy, 2-naphthyloxy and the like can be mentioned.

Unless otherwise specified, as the "C_{7-16} aralkyloxy group" in the present specification, for example, benzyloxy, phenethyloxy and the like can be mentioned.

Unless otherwise specified, as the "optionally substituted mercapto group" in the present specification, for example, "mercapto group", "optionally substituted C_{1-10} alkylthio group", "optionally substituted heterocyclylthio group", "optionally substituted C_{6-14} arylthio group", "optionally substituted C_{7-16} aralkylthio group" and the like can be mentioned.

Unless otherwise specified, as the "C_{1-6} alkylthio group" in the present specification, for example, methylthio, ethylthio, propylthio, isopropylthio, butylthio, sec-butylthio, tert-butylthio and the like can be mentioned. As the "C_{1-10} alkylthio group" in the present specification, heptylthio, octylthio, nonylthio, decylthio and the like can be mentioned besides the above-mentioned C_{1-6} alkylthio group.

Unless otherwise specified, as the "heterocyclylthio group" in the present specification, mercapto group substituted by a "heterocyclic group" below can be mentioned. As preferable examples of the heterocyclylthio group, tetrahydropyranylthio, thiazolylthio, pyridylthio, pyrazolylthio, oxazolylthio, thienylthio, furylthio and the like can be mentioned.

Unless otherwise specified, as the "C_{6-14} arylthio group" in the present specification, for example, phenylthio, 1-naphthylthio, 2-naphthylthio and the like can be mentioned.

Unless otherwise specified, as the "C_{7-16} aralkylthio group" in the present specification, for example, benzylthio, phenethylthio and the like can be mentioned.

Unless otherwise specified, as the "heterocyclic group" in the present specification, for example, a 5- to 14-membered (monocyclic, bicyclic or tricyclic) heterocyclic group containing one or two kind(s) of 1 to 4 heteroatom(s) selected from a nitrogen atom, a sulfur atom and an oxygen atom as a ring-constituting atom, besides carbon atoms, preferably (i) 5- to 14-membered (preferably 5- to 10-membered) aromatic heterocyclic group, (ii) 5- to 10-membered non-aromatic heterocyclic group and the like can be mentioned. Of these, 5- or 6-membered aromatic heterocyclic group is preferable.

Specifically, aromatic heterocyclic group such as thienyl (e.g., 2-thienyl, 3-thienyl), furyl (e.g., 2-furyl, 3-furyl), pyridyl (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl), thiazolyl (e.g., 2-thiazolyl, 4-thiazolyl, 5-thiazolyl), oxazolyl (e.g., 2-oxazolyl, 4-oxazolyl, 5-oxazolyl), quinolyl (e.g., 2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 8-quinolyl), isoquinolyl (e.g., 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl), pyrazinyl, pyrimidinyl (e.g., 2-pyrimidinyl, 4-pyrimidinyl), pyrrolyl (e.g., 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl), imidazolyl (e.g., 1-imidazolyl, 2-imidazolyl, 4-imidazolyl), pyrazolyl (e.g., 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl), pyridazinyl (e.g., 3-pyridazinyl, 4-pyridazinyl), isothiazolyl (e.g., 3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl), isoxazolyl (e.g., 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl), indolyl (e.g., 1-indolyl, 2-indolyl, 3-indolyl), 2-benzothiazolyl, 2-benzoxazolyl, benzimidazolyl (e.g., 1-benzimidazolyl, 2-benzimidazolyl), benzo[b]thienyl (e.g., 2-benzo[b]thienyl, 3-benzo[b]thienyl), benzo[b]furanyl (e.g., 2-benzo[b]furanyl, 3-benzo[b]furanyl) and the like;
non-aromatic heterocyclic group such as pyrrolidinyl (e.g., 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl), oxazolidinyl

(e.g., 2-oxazolidinyl), imidazolinyl (e.g., 1-imidazolinyl, 2-imidazolinyl, 4-imidazolinyl), piperidinyl (e.g., 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl), piperazinyl (e.g., 1-piperazinyl, 2-piperazinyl), morpholinyl (e.g., 2-morpholinyl, 3-morpholinyl, 4-morpholinyl), thiomorpholinyl (e.g., 2-thiomorpholinyl, 3-thiomorpholinyl, 4-thiomorpholinyl), tetrahydropyranyl and the like,
and the like can be mentioned.

Unless otherwise specified, as the "C_{1-6} alkylsulfonyl group" in the present specification, for example, methylsulfonyl, ethylsulfonyl and the like can be mentioned.

Unless otherwise specified, as the "C_{1-6} alkylsulfinyl group" in the present specification, for example, methylsulfinyl, ethylsulfinyl and the like can be mentioned.

Unless otherwise specified, as the "C_{6-14} arylsulfonyl group" in the present specification, for example, phenylsulfonyl, 1-naphthylsulfonyl, 2-naphthylsulfonyl and the like can be mentioned.

Unless otherwise specified, as the "C_{6-14} arylsulfinyl group" in the present specification, for example, phenylsulfinyl, 1-naphthylsulfinyl, 2-naphthylsulfinyl and the like can be mentioned.

Unless otherwise specified, as the "optionally esterified carboxyl group" in the present specification, for example, carboxyl, C_{1-6} alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl etc.), C_{6-14} aryloxy-carbonyl group (e.g., phenoxycarbonyl etc.), C_{7-16} aralkyloxy-carbonyl group (e.g., benzyloxycarbonyl, phenethyloxycarbonyl etc.) and the like can be mentioned.

Unless otherwise specified, as the "optionally halogenated C_{1-6} alkyl group" in the present specification, the above-mentioned "C_{1-6} alkyl group" optionally substituted by 1 to 5 above-mentioned "halogen atoms" can be mentioned. For example,

methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, isobutyl, trifluoromethyl and the like can be mentioned.

Unless otherwise specified, as the "optionally halogenated C_{1-6} alkoxy group" in the present specification, the above-mentioned "C_{1-6} alkoxy group" optionally substituted by 1 to 5 above-mentioned "halogen atoms" can be mentioned. For example, methoxy, ethoxy, isopropoxy, tert-butoxy, trifluoromethoxy and the like can be mentioned.

Unless otherwise specified, as the "mono- or di-C_{1-6} alkyl-amino group" in the present specification, amino group mono- or di-substituted by the above-mentioned "C_{1-6} alkyl group" can be mentioned. For example, methylamino, ethylamino, propylamino, dimethylamino, diethylamino and the like can be mentioned.

Unless otherwise specified, as the "mono- or di-C_{6-14} aryl-amino group" in the present specification, amino group mono- or di-substituted by the above-mentioned "C_{6-14} aryl group" can be mentioned. For example, phenylamino, diphenylamino, 1-naphthylamino, 2-naphthylamino and the like can be mentioned.

Unless otherwise specified, as the "mono- or di-C_{7-16} aralkyl-amino group" in the present specification, amino group mono- or di-substituted by the above-mentioned "C_{7-16} aralkyl group" can be mentioned. For example, benzylamino, phenethylamino and the like can be mentioned.

Unless otherwise specified, as the "N-C_{1-6} alkyl-N-C_{6-14} aryl-amino group" in the present specification, amino group substituted by the above-mentioned "C_{1-6} alkyl group" and the above-mentioned "C_{6-14} aryl group" can be mentioned. For example, N-methyl-N-phenylamino, N-ethyl-N-phenylamino and the like can be mentioned.

Unless otherwise specified, as the "N-C_{1-6} alkyl-N-C_{7-16} aralkyl-amino group" in the present specification, amino group substituted by the above-mentioned "C_{1-6} alkyl group" and the above-mentioned "C_{7-16} aralkyl group" can be mentioned. For

example, N-methyl-N-benzylamino, N-ethyl-N-benzylamino and the like can be mentioned.

Unless otherwise specified, as the "mono- or di-C_{1-6} alkyl-carbamoyl group" in the present specification, carbamoyl group mono- or di-substituted by the above-mentioned "C_{1-6} alkyl group" can be mentioned. For example, methylcarbamoyl, ethylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl and the like can be mentioned.

Unless otherwise specified, as the "mono- or di-C_{6-14} aryl-carbamoyl group" in the present specification, carbamoyl group mono- or di-substituted by the above-mentioned "C_{6-14} aryl group" can be mentioned. For example, phenylcarbamoyl, 1-naphthylcarbamoyl, 2-naphthylcarbamoyl and the like can be mentioned.

Unless otherwise specified, as the "mono- or di-5- to 7-membered heterocyclyl-carbamoyl group" in the present specification, carbamoyl group mono- or di-substituted by 5- to 7-membered heterocyclic group can be mentioned. As the 5- to 7-membered heterocyclic group, a heterocyclic group containing one or two kind(s) of 1 to 4 heteroatom(s) selected from a nitrogen atom, a sulfur atom and an oxygen atom as a ring-constituting atom, besides carbon atoms can be mentioned. As preferable examples of the "mono- or di-5 to 7-membered heterocyclyl-carbamoyl group", 2-pyridylcarbamoyl, 3-pyridylcarbamoyl, 4-pyridylcarbamoyl, 2-thienylcarbamoyl, 3-thienylcarbamoyl and the like can be mentioned.

Unless otherwise specified, as the "mono- or di-C_{1-6} alkyl-sulfamoyl group" in the present specification, sulfamoyl group mono- or di-substituted by the above-mentioned "C_{1-6} alkyl group" can be used, for example, methylsulfamoyl, ethylsulfamoyl, dimethylsulfamoyl, diethylsulfamoyl and the like can be mentioned.

Unless otherwise specified, as the "mono- or di-C_{6-14} aryl-sulfamoyl group" in the present specification, sulfamoyl group

mono- or di-substituted by the above-mentioned "C_{6-14} aryl group" can be used, for example, phenylsulfamoyl, diphenylsulfamoyl, 1-naphthylsulfamoyl, 2-naphthylsulfamoyl and the like can be mentioned.

Unless otherwise specified, as the "optionally substituted C_{1-6} alkyl group", "optionally substituted C_{2-6} alkenyl group", "optionally substituted C_{2-6} alkynyl group", "optionally substituted C_{1-10} alkoxy group (containing optionally substituted C_{1-6} alkoxy group)" and "optionally substituted C_{1-10} alkylthio group (containing optionally substituted C_{1-6} alkylthio group)" in the present specification, for example, "C_{1-6} alkyl group", "C_{2-6} alkenyl group", "C_{2-6} alkynyl group", "C_{1-10} alkoxy group (containing C_{1-6} alkoxy group)" and "C_{1-10} alkylthio group (containing C_{1-6} alkylthio group)", each of which optionally has 1 to 5 substituent(s) at substitutable position(s) selected from
(1) halogen atom; (2) hydroxy group; (3) amino group; (4) nitro group; (5) cyano group; (6) heterocyclic group (preferably furyl, pyridyl, thienyl, pyrazolyl, thiazolyl, oxazolyl) optionally substituted by 1 to 3 substituent(s) selected from halogen atom, hydroxy group, amino group, nitro group, cyano group, optionally halogenated C_{1-6} alkyl group, mono- or di-C_{1-6} alkyl-amino group, C_{6-14} aryl group, mono- or di-C_{6-14} aryl-amino group, C_{3-8} cycloalkyl group, C_{1-6} alkoxy group, C_{1-6} alkylthio group, C_{1-6} alkylsulfinyl group, C_{1-6} alkylsulfonyl group, optionally esterified carboxyl group, carbamoyl group, thiocarbamoyl group, mono- or di-C_{1-6} alkyl-carbamoyl group, mono- or di-C_{6-14} aryl-carbamoyl group, sulfamoyl group, mono- or di-C_{1-6} alkyl-sulfamoyl group and mono- or di-C_{6-14} aryl-sulfamoyl group; (7) mono- or di-C_{1-6} alkyl-amino group; (8) mono- or di-C_{6-14} aryl-amino group; (9) mono- or di-C_{7-16} aralkyl-amino group; (10) N-C_{1-6} alkyl-N-C_{6-14} aryl-amino group; (11) N-C_{1-6} alkyl-N-C_{7-16} aralkyl-amino group; (12) C_{3-8} cycloalkyl group; (13) optionally halogenated C_{1-6} alkoxy group; (14) C_{1-6} alkylthio group;

(15) C_{1-6} alkylsulfinyl group; (16) C_{1-6} alkylsulfonyl group; (17) optionally esterified carboxyl group; (18) carbamoyl group; (19) thiocarbamoyl group; (20) mono- or di-C_{1-6} alkyl-carbamoyl group; (21) mono- or di-C_{6-14} aryl-carbamoyl group; (22) mono- or di-5- to 7-membered heterocyclyl-carbamoyl group; (23) C_{1-6} alkyl-carbonylamino group (e.g., acetylamino, propionylamino) optionally substituted by carboxyl group; (24) C_{6-14} aryloxy group optionally substituted by 1 to 3 substituent(s) selected from halogen atom, hydroxy group, amino group, nitro group, cyano group, optionally halogenated C_{1-6} alkyl group, mono- or di-C_{1-6} alkyl-amino group, C_{6-14} aryl group, mono- or di-C_{6-14} aryl-amino group, C_{3-8} cycloalkyl group, C_{1-6} alkoxy group, C_{1-6} alkylthio group, C_{1-6} alkylsulfinyl group, C_{1-6} alkylsulfonyl group, optionally esterified carboxyl group, carbamoyl group, thiocarbamoyl group, mono- or di-C_{1-6} alkyl-carbamoyl group, mono- or di-C_{6-14} aryl-carbamoyl group, sulfamoyl group, mono- or di-C_{1-6} alkyl-sulfamoyl group and mono- or di-C_{6-14} aryl-sulfamoyl group; (25) C_{6-14} aryl group optionally substituted by 1 to 3 substituent(s) selected from halogen atom, hydroxy group, amino group, nitro group, cyano group, optionally halogenated C_{1-6} alkyl group, mono- or di-C_{1-6} alkyl-amino group, C_{6-14} aryl group, mono- or di-C_{6-14} aryl-amino group, C_{3-8} cycloalkyl group, C_{1-6} alkoxy group, C_{1-6} alkylthio group, C_{1-6} alkylsulfinyl group, C_{1-6} alkylsulfonyl group, optionally esterified carboxyl group, carbamoyl group, thiocarbamoyl group, mono- or di-C_{1-6} alkyl-carbamoyl group, mono- or di-C_{6-14} aryl-carbamoyl group, sulfamoyl group, mono- or di-C_{1-6} alkyl-sulfamoyl group and mono- or di-C_{6-14} aryl-sulfamoyl group; (26) heterocyclyloxy group; (27) sulfamoyl group; (28) mono- or di-C_{1-6} alkyl-sulfamoyl group; (29) mono- or di-C_{6-14} aryl-sulfamoyl group; (30) C_{7-16} aralkyloxy group optionally substituted by 1 to 3 substituent(s) selected from halogen atom, hydroxy group, amino group, nitro group, cyano group, optionally halogenated C_{1-6} alkyl group, mono- or di-C_{1-6} alkyl-amino group, C_{6-14} aryl group, mono- or di-C_{6-14} aryl-amino

group, C_{3-8} cycloalkyl group, C_{1-6} alkoxy group, C_{1-6} alkylthio group, C_{1-6} alkylsulfinyl group, C_{1-6} alkylsulfonyl group, optionally esterified carboxyl group, carbamoyl group, thiocarbamoyl group, mono- or di-C_{1-6} alkyl-carbamoyl group, mono- or di-C_{6-14} aryl-carbamoyl group, sulfamoyl group, mono- or di-C_{1-6} alkyl-sulfamoyl group and mono- or di-C_{6-14} aryl-sulfamoyl group; and the like,

can be mentioned.

As the "optionally substituted C_{3-8} cycloalkyl group", "optionally substituted C_{6-14} aryl group", "optionally substituted C_{7-16} aralkyl group", "optionally substituted heterocyclic group", "optionally substituted heterocyclyloxy group", "optionally substituted C_{6-14} aryloxy group", "optionally substituted C_{7-16} aralkyloxy group", "optionally substituted heterocyclylthio group", "optionally substituted C_{6-14} arylthio group" and "optionally substituted C_{7-16} aralkylthio group" in the present specification, for example,

"C_{3-8} cycloalkyl group", "C_{6-14} aryl group", "C_{7-16} aralkyl group", "heterocyclic group", "heterocyclyloxy group", "C_{6-14} aryloxy group", "C_{7-16} aralkyloxy group", "heterocyclylthio group", "C_{6-14} arylthio group" and "C_{7-16} aralkylthio group", each of which optionally has 1 to 5 substituent(s) at substitutable position(s) selected from

(1) halogen atom; (2) hydroxy group; (3) amino group; (4) nitro group; (5) cyano group; (6) optionally substituted C_{1-6} alkyl group; (7) optionally substituted C_{2-6} alkenyl group; (8) optionally substituted C_{2-6} alkynyl group; (9) C_{6-14} aryl group optionally substituted by 1 to 3 substituent(s) selected from halogen atom, hydroxy group, amino group, nitro group, cyano group, optionally halogenated C_{1-6} alkyl group, mono- or di-C_{1-6} alkyl-amino group, C_{6-14} aryl group, mono- or di-C_{6-14} aryl-amino group, C_{3-8} cycloalkyl group, C_{1-6} alkoxy group, C_{1-6} alkylthio group, C_{1-6} alkylsulfinyl group, C_{1-6} alkylsulfonyl group, optionally esterified carboxyl group, carbamoyl group,

thiocarbamoyl group, mono- or di-C_{1-6} alkyl-carbamoyl group, mono- or di-C_{6-14} aryl-carbamoyl group, sulfamoyl group, mono- or di-C_{1-6} alkyl-sulfamoyl group and mono- or di-C_{6-14} aryl-sulfamoyl group; (10) C_{6-14} aryloxy group optionally substituted by 1 to 3 substituent(s) selected from halogen atom, hydroxy group, amino group, nitro group, cyano group, optionally halogenated C_{1-6} alkyl group, mono- or di-C_{1-6} alkyl-amino group, C_{6-14} aryl group, mono- or di-C_{6-14} aryl-amino group, C_{3-8} cycloalkyl group, C_{1-6} alkoxy group, C_{1-6} alkylthio group, C_{1-6} alkylsulfinyl group, C_{1-6} alkylsulfonyl group, optionally esterified carboxyl group, carbamoyl group, thiocarbamoyl group, mono- or di-C_{1-6} alkyl-carbamoyl group, mono- or di-C_{6-14} aryl-carbamoyl group, sulfamoyl group, mono- or di-C_{1-6} alkyl-sulfamoyl group and mono- or di-C_{6-14} aryl-sulfamoyl group; (11) C_{7-16} aralkyloxy group optionally substituted by 1 to 3 substituent(s) selected from halogen atom, hydroxy group, amino group, nitro group, cyano group, optionally halogenated C_{1-6} alkyl group, mono- or di-C_{1-6} alkyl-amino group, C_{6-14} aryl group, mono- or di-C_{6-14} aryl-amino group, C_{3-8} cycloalkyl group, C_{1-6} alkoxy group, C_{1-6} alkylthio group, C_{1-6} alkylsulfinyl group, C_{1-6} alkylsulfonyl group, optionally esterified carboxyl group, carbamoyl group, thiocarbamoyl group, mono- or di-C_{1-6} alkyl-carbamoyl group, mono- or di-C_{6-14} aryl-carbamoyl group, sulfamoyl group, mono- or di-C_{1-6} alkyl-sulfamoyl group and mono- or di-C_{6-14} aryl-sulfamoyl group; (12) heterocyclic group (preferably furyl, pyridyl, thienyl, pyrazolyl, thiazolyl, oxazolyl) optionally substituted by 1 to 3 substituent(s) selected from halogen atom, hydroxy group, amino group, nitro group, cyano group, optionally halogenated C_{1-6} alkyl group, mono- or di-C_{1-6} alkyl-amino group, C_{6-14} aryl group, mono- or di-C_{6-14} aryl-amino group, C_{3-8} cycloalkyl group, C_{1-6} alkoxy group, C_{1-6} alkylthio group, C_{1-6} alkylsulfinyl group, C_{1-6} alkylsulfonyl group, optionally esterified carboxyl group, carbamoyl group, thiocarbamoyl group, mono- or di-C_{1-6} alkyl-carbamoyl group, mono- or di-C_{6-14} aryl-carbamoyl group, sulfamoyl

group, mono- or di-C_{1-6} alkyl-sulfamoyl group and mono- or di-C_{6-14} aryl-sulfamoyl group; (13) mono- or di-C_{1-6} alkyl-amino group; (14) mono- or di-C_{6-14} aryl-amino group; (15) mono- or di-C_{7-16} aralkyl-amino group; (16) N-C_{1-6} alkyl-N-C_{6-14} aryl-amino group; (17) N-C_{1-6} alkyl-N-C_{7-16} aralkyl-amino group; (18) C_{3-8} cycloalkyl group; (19) optionally substituted C_{1-6} alkoxy group; (20) C_{1-6} alkylthio group; (21) C_{1-6} alkylsulfinyl group; (22) C_{1-6} alkylsulfonyl group; (23) optionally esterified carboxyl group; (24) carbamoyl group; (25) thiocarbamoyl group; (26) mono- or di-C_{1-6} alkyl-carbamoyl group; (27) mono- or di-C_{6-14} aryl-carbamoyl group; (28) mono- or di-5- to 7-membered heterocyclyl-carbamoyl group; (29) sulfamoyl group; (30) mono- or di-C_{1-6} alkyl-sulfamoyl group; (31) mono- or di-C_{6-14} aryl-sulfamoyl group; and the like,

can be mentioned.

Unless otherwise specified, as the "optionally substituted amino group" in the present specification, amino group optionally substituted by 1 or 2 substituent(s) selected from (1) optionally substituted C_{1-6} alkyl group; (2) optionally substituted C_{2-6} alkenyl group; (3) optionally substituted C_{2-6} alkynyl group; (4) optionally substituted C_{3-8} cycloalkyl group; (5) optionally substituted C_{6-14} aryl group; (6) optionally substituted C_{1-6} alkoxy group; (7) optionally substituted acyl group; (8) optionally substituted heterocyclic group (preferably furyl, pyridyl, thienyl, pyrazolyl, thiazolyl, oxazolyl); (9) sulfamoyl group; (10) mono- or di-C_{1-6} alkyl-sulfamoyl group; (11) mono- or di-C_{6-14} aryl-sulfamoyl group; and the like, can be mentioned. When the "optionally substituted amino group" is an amino group substituted by 2 substituents, these substituents may form a nitrogen-containing heterocycle together with the adjacent nitrogen atom. As the "nitrogen-containing heterocycle", for example, a 5- to 7-membered nitrogen-containing heterocycle containing at least one nitrogen atom and optionally further containing 1 or 2 heteroatom(s) selected from

an oxygen atom, a sulfur atom and a nitrogen atom as a ring-constituting atom, besides carbon atoms can be mentioned. As preferable examples of the nitrogen-containing heterocycle, pyrrolidine, imidazolidine, pyrazolidine, piperidine, piperazine, morpholine, thiomorpholine, thiazolidine, oxazolidine and the like can be mentioned.

Unless otherwise specified, as the "optionally substituted acyl group" in the present specification, groups represented by the formula : $-COR^8$, $-CO-OR^8$, $-SO_2R^8$, $-SOR^8$, $-PO(OR^8)(OR^9)$, $-CO-NR^{8a}R^{9a}$ and $-CS-NR^{8a}R^{9a}$, wherein R^8 and R^9 are the same or different and each is a hydrogen atom, an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group, and R^{8a} and R^{9a} are the same or different and each is a hydrogen atom, an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group, or R^{8a} and R^{9a} may form an optionally substituted nitrogen-containing heterocycle together with the adjacent nitrogen atom, and the like can be mentioned.

As the "nitrogen-containing heterocycle" of the "optionally substituted nitrogen-containing heterocycle" which R^{8a} and R^{9a} form together with the adjacent nitrogen atom, for example, a 5- to 7-membered nitrogen-containing heterocycle containing at least one nitrogen atom and optionally further containing 1 to 2 heteroatom(s) selected from an oxygen atom, a sulfur atom and a nitrogen atom as a ring-constituting atom, besides carbon atoms can be mentioned. As preferable examples of the "nitrogen-containing heterocycle", pyrrolidine, imidazolidine, pyrazolidine, piperidine, piperazine, morpholine, thiomorpholine, thiazolidine, oxazolidine and the like can be mentioned.

The nitrogen-containing heterocycle optionally has 1 to 2 substituent(s) at substitutable position(s). As these substituent(s), a hydroxy group, an optionally halogenated C_{1-6}

alkyl group, a C_{6-14} aryl group, a C_{7-16} aralkyl group and the like can be mentioned.

As preferable examples of "optionally substituted acyl group", formyl group, carboxyl group, carbamoyl group, C_{1-6} alkyl-carbonyl group (e.g., acetyl, isobutanoyl, isopentanoyl), C_{1-6} alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl), C_{3-8} cycloalkyl-carbonyl group (e.g., cyclopentylcarbonyl, cyclohexylcarbonyl), C_{6-14} aryl-carbonyl group (e.g., benzoyl, 1-naphthoyl, 2-naphthoyl), C_{7-16} aralkyl-carbonyl group (e.g., phenylacetyl, 2-phenylpropanoyl), C_{6-14} aryloxy-carbonyl group (e.g., phenyloxycarbonyl, naphthyloxycarbonyl), C_{7-16} aralkyloxy-carbonyl group (e.g., benzyloxycarbonyl, phenethyloxycarbonyl), mono- or di-C_{1-6} alkylcarbamoyl group, mono- or di-C_{6-14} aryl-carbamoyl group, C_{3-8} cycloalkyl-carbamoyl group (e.g., cyclopropylcarbamoyl), C_{7-16} aralkyl-carbamoyl group (e.g., benzylcarbamoyl), C_{1-6} alkylsulfonyl group, C_{6-14} arylsulfonyl group, nitrogen-containing heterocyclyl-carbonyl group (e.g., pyrrolidinylcarbonyl, piperidinylcarbonyl), C_{1-6} alkylsulfinyl group, C_{6-14} arylsulfinyl group, thiocarbamoyl group, sulfamoyl group, mono- or di-C_{1-6} alkyl-sulfamoyl group, mono- or di-C_{6-14} aryl-sulfamoyl group, mono- or di-C_{7-16} aralkyl-sulfamoyl group (e.g., benzylsulfamoyl) and the like can be mentioned.

The "C_{1-4} alkylene group" of the "optionally substituted C_{1-4} alkylene group" in the present specification is straight-chain or branched, and, for example, methylene, ethylene, 1-methylethylene, propylene, 1-ethylethylene, 1-methylpropylene, 2-methylpropylene, butylene and the like can be mentioned. The C_{1-4} alkylene group optionally has 1 to 3 substituent(s) at substitutable position(s). As these substituent(s), for example, halogen atom, hydroxy group, amino group, mono- or di-C_{1-6} alkyl-amino group, mono- or di-C_{6-14} aryl-amino group, mono- or di-C_{7-16} aralkyl-amino group, nitro group, cyano group, C_{1-6} alkoxy group, C_{1-6} alkylthio group and the like can be mentioned.

As the "C_{1-3} alkylene group" of the "optionally substituted C_{1-3} alkylene group" in the present specification, of the aforementioned "C_{1-4} alkylene groups", those having 1 to 3 carbon atom(s) can be mentioned. The C_{1-3} alkylene group optionally has 1 to 3 substituent(s) at substitutable position(s). As these substituent(s), those exemplarily shown as the substituent of the above-mentioned C_{1-4} alkylene group can be mentioned.

The compound represented by the formula (I) of the present invention (hereinafter sometimes to be abbreviated as compound (I)) and a salt thereof are explained in the following.

R^2 in the formula (I) is a halogen atom, an optionally substituted hydrocarbon group, an optionally substituted hydroxy group, an optionally substituted amino group, an optionally substituted mercapto group or an optionally substituted heterocyclic group, preferably an optionally substituted hydrocarbon group or an optionally substituted hydroxy group.

R^1 and R^3 in the formula (I) are the same (except when R^1 and R^3 are both hydrogen atoms) or different and each is a hydrogen atom, a halogen atom, an optionally substituted hydrocarbon group or an optionally substituted hydroxy group, preferably a hydrogen atom, a halogen atom or a C_{1-6} alkyl group, more preferably a halogen atom or a C_{1-6} alkyl group.

R^4 and R^5 in the formula (I) are the same or different and each is a hydrogen atom, a halogen atom, an optionally substituted hydrocarbon group or an optionally substituted hydroxy group, preferably a hydrogen atom or a halogen atom.

E in the formula (I) is a bond, an optionally substituted C_{1-4} alkylene group, $-W^1-O-W^2-$, $-W^1-S-W^2-$ or $-W^1-N(R^6)-W^2-$ (W^1 and W^2 are the same or different and each is a bond or an optionally substituted C_{1-3} alkylene group, and R^6 is a hydrogen atom, an optionally substituted acyl group or an optionally substituted hydrocarbon group), preferably a bond.

Ring S^1 in the formula (I) is a benzene ring optionally further having substituent(s) selected from a halogen atom, an

optionally substituted hydrocarbon group, an optionally substituted hydroxy group and an optionally substituted amino group, preferably a benzene ring optionally further having a C_{1-6} alkoxy group. The number of the substituent is, for example, 1 or 2.

R in the formula (I) is an optionally substituted hydroxy group or an optionally substituted amino group, preferably an optionally substituted hydroxy group, more preferably a hydroxy group or a C_{1-6} alkoxy group. Of these, a hydroxy group is preferable.

As the "preferable examples of compound (I)", the following compounds can be mentioned.

A compound wherein

R^2 is

(1) halogen atom,

(2) C_{1-6} alkyl group optionally substituted by C_{6-14} aryloxy group optionally substituted by halogen atom,

(3) hydroxy group,

(4) C_{1-10} alkoxy group optionally substituted by 1 to 3 substituent(s) selected from

(a) 5- to 7-membered heterocyclic group containing one or two kind(s) of 1 to 4 heteroatom(s) selected from a nitrogen atom, a sulfur atom and an oxygen atom as a ring-constituting atom, besides carbon atom (preferably, pyridyl, thiazolyl), optionally substituted by optionally halogenated C_{1-6} alkyl group,

(b) C_{3-8} cycloalkyl group,

(c) hydroxy group,

(d) optionally halogenated C_{1-6} alkoxy group,

(e) amino group, and

(f) mono- or di-C_{1-6} alkyl-amino group,

(5) heterocyclyloxy group (preferably tetrahydropyranyloxy), or

(6) C_{7-16} aralkyloxy group;

R^1 and R^3 are the same (except when R^1 and R^3 are both hydrogen atoms) or different and each is hydrogen atom, halogen atom or C_{1-6} alkyl group;

R^4 and R^5 are the same or different and each is hydrogen atom or halogen atom;

E is bond;

ring S^1 is benzene ring optionally further having C_{1-6} alkoxy group; and

R is hydroxy group or C_{1-6} alkoxy group (preferably hydroxy group).

As a salt of a compound used in the present invention, for example, metal salts, ammonium salts, salts with organic bases, salts with inorganic acids, salts with organic acids, salts with basic or acidic amino acids and the like. Preferable examples of the metal salt include alkali metal salts such as sodium salt, potassium salt and the like; alkaline earth metal salts such as calcium salt, magnesium salt, barium salt and the like; aluminum salt, and the like. Preferable examples of the salt with organic base include a salt with trimethylamine, triethylamine, pyridine, picoline, 2,6-lutidine, ethanolamine, diethanolamine, triethanolamine, cyclohexylamine, dicyclohexylamine, N,N-dibenzylethylenediamine and the like. Preferable examples of the salt with inorganic acid include a salt with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like. Preferable examples of the salt with organic acid include a salt with formic acid, acetic acid, trifluoroacetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like. Preferable examples of the salt with basic amino acid include a salt with arginine, lysin, ornithine and the like. Preferable examples of the salt with acidic amino acid include a salt with aspartic acid, glutamic acid and the like.

Of these, a pharmacologically acceptable salt is preferable. For example, when the compound has an acidic functional group, metal salts such as alkali metal salts (e.g., sodium salt, potassium salt etc.), alkaline earth metal salts (e.g., calcium salt, magnesium salt, barium salt etc.) and the like, ammonium salt and the like are preferable, and when the compound has basic functional group, salts with inorganic acid such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like; or salts with organic acid such as acetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, p-toluenesulfonic acid and the like are preferable.

A prodrug of compound (I) and a salt thereof is a compound that converts to compound (I) due to the reaction by enzyme, gastric acid and the like under the physiological conditions in the body; that is, a compound that converts to compound (I) by enzymatic oxidation, reduction, hydrolysis and the like, and a compound that converts to compound (I) by hydrolysis and the like by gastric acid and the like.

Examples of a prodrug of compound (I) include a compound wherein an amino group of compound (I) is acylated, alkylated or phosphorylated (e.g., compound where amino group of compound (I) is eicosanoylated, alanylated, pentylaminocarbonylated, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylated, tetrahydrofuranylated, pyrrolidylmethylated, pivaloyloxymethylated, tert-butylated and the like); a compound wherein a hydroxy group of compound (I) is acylated, alkylated, phosphorylated or borated (e.g., a compound where a hydroxy group of compound (I) is acetylated, palmitoylated, propanoylated, pivaloylated, succinylated, fumarylated, alanylated, dimethylaminomethylcarbonylated and the like); a compound wherein a carboxyl group of compound (I) is esterified or amidated (e.g., a compound where a carboxyl group of compound

(I) is C_{1-6} alkyl esterified, phenyl esterified, carboxymethyl esterified, dimethylaminomethyl esterified, pivaloyloxymethyl esterified, ethoxycarbonyloxyethyl esterified, phthalidyl esterified, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl esterified, cyclohexyloxycarbonylethyl esterified, methylamidated and the like) and the like. Of these, a compound wherein a carboxyl group of compound (I) is esterified by C_{1-6} alkyl group such as methyl, ethyl, tert-butyl and the like is preferable. These compounds can be produced from compound (I) by a method known *per se*.

A prodrug of compound (I) may be a compound that converts to compound (I) under physiological conditions as described in Development of Pharmaceutical Products, vol. 7, Molecule Design, 163-198, Hirokawa Shoten (1990).

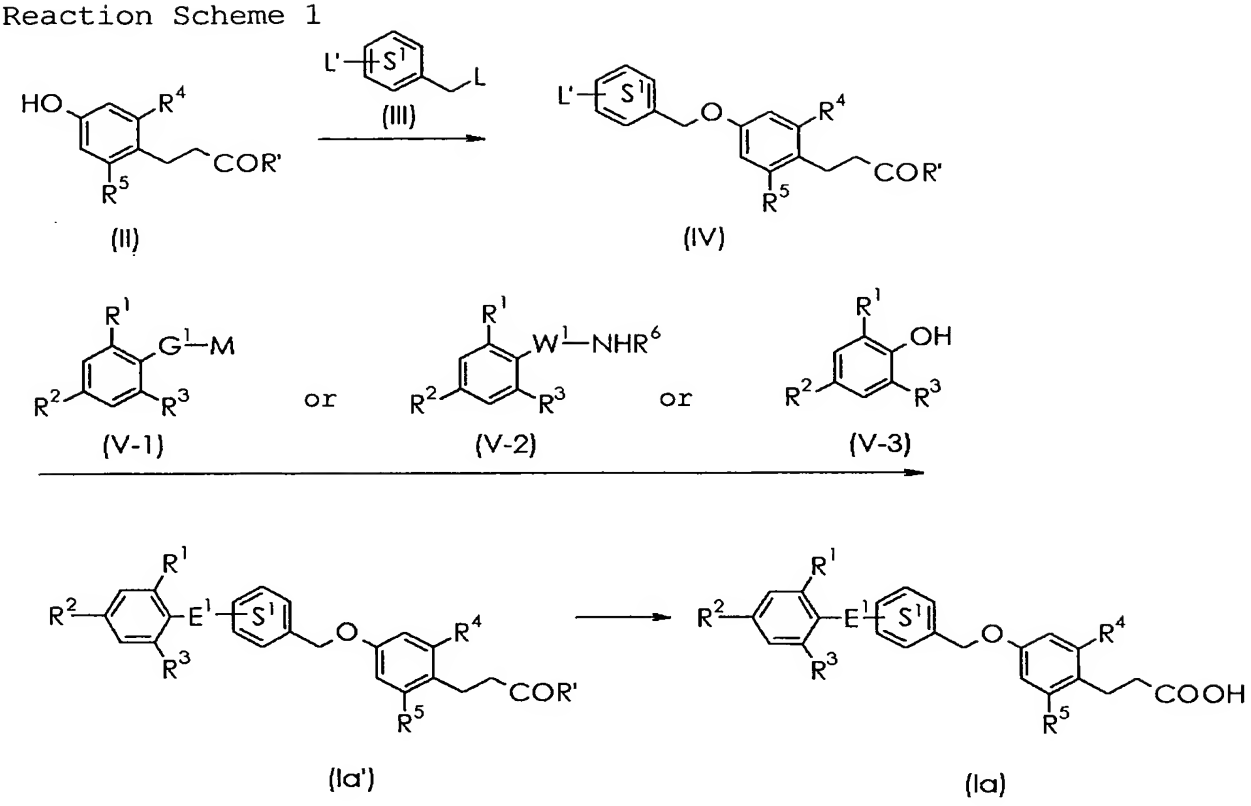
Hereinafter the production methods of the compound (I) or a salt thereof of the present invention are explained.

Each symbol of the compounds in the schematic drawings of the following reaction schemes is as defined above unless particularly described. Each compound described in the reaction schemes may form a salt as long as it does not inhibit the reaction, and as such salt, those similar to the salts of compound (I) can be mentioned.

Compound (I) can be produced, for example, according to the method shown by the following reaction schemes 1-4.

Compound (I) wherein E is E^1 (E^1 is a bond, an optionally substituted C_{1-4} alkylene group, $-W^1-N(R^6)-$ (W^1 and R^6 are as defined above) or -O-) (compounds represented by the formulas (Ia') and (Ia) (to be abbreviated as compound (Ia') and compound (Ia), respectively)) can be produced, for example, according the method shown by the following Reaction Scheme 1 or a method analogous thereto.

Reaction Scheme 1



wherein R' is an optionally substituted C_{1-6} alkoxy group, L is a leaving group or a hydroxy group, L' is a leaving group, M is a metal (e.g., potassium, sodium, lithium, magnesium, copper, mercury, zinc, thallium, boron, tin and the like, which may be formed into a complex), G^1 is a bond or an optionally substituted C_{1-4} alkylene group (same as optionally substituted C_{1-4} alkylene group for E), and the other symbols are as defined above.

As the "leaving group" for L and L', for example, a halogen atom (e.g., fluorine, chlorine, bromine, iodine), an optionally halogenated C_{1-6} alkylsulfonyloxy group (e.g., methanesulfonyloxy, ethanesulfonyloxy, trichloromethanesulfonyloxy, trifluoromethanesulfonyloxy), a C_{6-10} arylsulfonyloxy group optionally having substituent(s) (e.g., C_{6-10} arylsulfonyloxy group (e.g., phenylsulfonyloxy, naphthylsulfonyloxy) optionally having 1 to 3 substituent(s) selected from C_{1-6} alkyl group (e.g., methyl, ethyl), C_{1-6} alkoxy group (e.g., methoxy, ethoxy) and nitro, and the like; as

specific examples, phenylsulfonyloxy group, m-nitrophenylsulfonyloxy group, p-toluenesulfonyloxy group and the like) and the like can be mentioned.

The compounds represented by the formulas (II), (III), (V-1), (V-2) and (V-3) (to be abbreviated as compounds (II), (III), (V-1), (V-2) and (V-3), respectively) are commercially available, and can be also produced according a method known *per se* or a method analogous thereto.

A compound represented by the formula (IV) (to be abbreviated as compound (IV)) can be produced by reacting compound (II) with compound (III).

(i) When L is a hydroxy group, compound (IV) can be produced by subjecting compound (II) and compound (III) to Mitsunobu reaction (Synthesis, 1981, pages 1-27). In the reaction, compound (II) and compound (III) are reacted in the presence of azodicarboxylates such as diethyl azodicarboxylate, diisopropyl azodicarboxylate, 1,1'-(azodicarbonyl)dipiperidine and the like and phosphines such as triphenylphosphine, tributylphosphine and the like.

The reaction is advantageously carried out using a solvent inert to the reaction. While the solvent is not particularly limited as long as the reaction proceeds, for example, solvents such as ethers (e.g., diethyl ether, diisopropyl ether, diphenyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like); aromatic hydrocarbons (e.g., benzene, toluene and the like); saturated hydrocarbons (e.g., cyclohexane, hexane and the like); amides (e.g., N,N-dimethylformamide, N,N-dimethylacetamide, hexamethylphosphoric triamide and the like); halogenated hydrocarbons (e.g., dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like); nitriles (e.g., acetonitrile, propionitrile and the like); ketones (e.g., acetone, ethyl methyl ketone and the like); sulfoxides (e.g., dimethyl sulfoxide and the like), and the like, or a mixed solvent thereof and the like are preferable.

The reaction time is generally about 5 min. to about 48 hrs., preferably about 10 min. to about 24 hrs. The reaction temperature is generally about -20 to about 200°C, preferably about 0 to about 100°C.

The amount of compound (III) to be used is about 1 to about 5 mol, preferably about 1 to about 2 mol relative to 1 mol of compound (II).

The amount of the "azodicarboxylate" and "phosphine" to be used is respectively about 1 to about 5 mol, preferably about 1 to about 2 mol, relative to 1 mol of compound (II).

(ii) When L is a leaving group, compound (IV) can be produced by reacting compound (II) with compound (III) in the presence of a base.

As the base, for example, alkali metal hydroxides such as sodium hydroxide, potassium hydroxide, lithium hydroxide and the like; alkaline earth metal hydroxides such as barium hydroxide and the like; alkali metal carbonates such as sodium carbonate, potassium carbonate, cesium carbonate and the like; alkali metal hydrogencarbonates such as sodium hydrogencarbonate and the like; acetates such as sodium acetate, ammonium acetate and the like; aromatic amines such as pyridine, lutidine and the like; tertiary amines such as triethylamine, tripropylamine, tributylamine, N-ethyldiisopropylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine and the like; alkali metal hydrides such as sodium hydride, potassium hydride and the like; metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide and the like; alkali metal alkoxides having 1 to 6 carbon atoms such as sodium methoxide, sodium ethoxide, sodium tert-butoxide, potassium tert-butoxide and the like, and the like can be mentioned.

The reaction is advantageously carried out using a solvent inert to the reaction. While the solvent is not particularly limited as long as the reaction proceeds, for example, solvents

such as ethers (e.g., diethyl ether, diisopropyl ether, diphenyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like); aromatic hydrocarbons (e.g., benzene, toluene and the like); saturated hydrocarbons (e.g., cyclohexane, hexane and the like); amides (e.g., N,N-dimethylformamide, N,N-dimethylacetamide, hexamethylphosphoric triamide and the like); halogenated hydrocarbons (e.g., dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like); nitriles (e.g., acetonitrile, propionitrile and the like); esters (e.g., methyl acetate, ethyl acetate, butyl acetate and the like); sulfoxides (e.g., dimethyl sulfoxide and the like); water and the like, or a mixed solvent thereof and the like are preferable.

The amount of compound (III) to be used is about 0.8 to 10 mol, preferably about 0.9 to 2 mol, relative to 1 mol of compound (II). The amount of the base to be used is about 1 to 10 mol, preferably about 1 to 3 mol, relative to 1 mol of compound (II).

The reaction time is generally about 10 min. to about 12 hrs., preferably about 20 min. to about 6 hrs. The reaction temperature is generally about -50 to about 150°C, preferably about -20 to about 100°C.

Compound (Ia') can be produced by reacting compound (IV) with compound (V-1) or compound (V-2) or compound (V-3) (unless otherwise specified, these are collectively referred to as compound (V)).

The reaction of compound (IV) with compound (V) is generally carried out in the presence of a base. As the base, alkali metal hydrides (e.g., sodium hydride, potassium hydride and the like); alkali metal hydroxides (e.g., lithium hydroxide, sodium hydroxide, potassium hydroxide and the like); alkaline earth metal hydroxides (e.g., magnesium hydroxide, calcium hydroxide and the like); alkali metal carbonates (e.g., sodium carbonate, potassium carbonate and the like); alkali metal hydrogencarbonates (e.g., sodium hydrogencarbonate, potassium

hydrogencarbonate and the like); alkali metal alkoxides having 1 to 6 carbon atoms (e.g., sodium methoxide, sodium ethoxide, sodium tert-butoxide and the like); organic bases (e.g., trimethylamine, triethylamine, diisopropylethylamine, pyridine, picoline, N-methylpyrrolidine, N-methylmorpholine, 1,5-diazabicyclo[4.3.0]-5-nonene, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]-7-undecene and the like); organic lithiums (e.g., methyllithium, n-butyllithium, sec-butyllithium, tert-butyllithium and the like); lithium amides (e.g., lithium diisopropylamide and the like), and the like can be mentioned.

The reaction of compound (IV) with compound (V) is advantageously carried out using a solvent inert to the reaction. While the solvent is not particularly limited as long as the reaction proceeds, solvents such as alcohols (e.g., methanol, ethanol, propanol, isopropanol, butanol, tert-butanol and the like); ethers (e.g., dioxane, tetrahydrofuran, diethyl ether, tert-butyl methyl ether, diisopropyl ether, ethyleneglycol-dimethylether and the like); esters (e.g., ethyl formate, ethyl acetate, n-butyl acetate and the like); halogenated hydrocarbons (e.g., dichloromethane, chloroform, carbon tetrachloride, trichloroethylene and the like); hydrocarbons (e.g., n-hexane, benzene, toluene and the like); amides (e.g., formamide, N,N-dimethylformamide, N,N-dimethylacetamide and the like); nitriles and the like (e.g., acetonitrile, propionitrile and the like); sulfoxides (e.g., dimethyl sulfoxide and the like); sulfolane; hexamethylphosphoramide; water and the like, a mixed solvent thereof and the like are preferable.

The reaction of compound (IV) with compound (V) can be generally promoted by the use of a metal catalyst. As the metal catalyst, metal complexes having various ligands can be used and, for example, palladium compounds [e.g., palladium(II) acetate, tetrakis(triphenylphosphine)palladium(0), bis(triphenylphosphine)palladium(II) chloride, dichlorobis(triethylphosphine)palladium(0),

tris(dibenzylideneacetone)dipalladium-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, a complex of palladium(II) acetate and 1,1'-bis(diphenylphosphino)ferrocene, and the like], nickel compounds [e.g., tetrakis(triphenylphosphine)nickel(0), bis(triethylphosphine)nickel(II) chloride, bis(triphenylphosphine)nickel(II) chloride and the like], rhodium compounds [e.g., tris(triphenylphosphine)rhodium(III) chloride and the like], cobalt compounds, copper compounds [e.g., copper oxide, copper(II) chloride and the like], platinum compounds and the like can be mentioned. Of these, palladium compounds, nickel compounds and copper compounds are preferable. The amount of the metal catalyst to be used is about 0.000001 to 5 mol, preferably about 0.0001 to 1 mol, relative to 1 mol of compound (IV). When a metal catalyst unstable to oxygen is used in this reaction, the reaction is preferably carried out in an inactive gas (e.g., argon gas or nitrogen gas) stream.

The amount of compound (V) to be used is about 0.8 to 10 mol, preferably about 0.9 to 2 mol, relative to 1 mol of compound (IV). The amount of the base to be used is about 1 to about 20 mol, preferably about 1 to about 5 mol, relative to 1 mol of compound (IV).

The reaction temperature is about -10°C to about 250°C, preferably about 0°C to about 150°C.

While the reaction time varies depending on the kinds of compound (IV), compound (V), metal catalyst, base and solvent, reaction temperature and the like, it is generally about 1 min. to about 200 hrs., preferably about 5 min. to about 100 hrs.

Compound (Ia) can be produced by subjecting compound (Ia') to hydrolysis reaction. The hydrolysis reaction is carried out using an acid or a base according to a conventional method.

As the acid, for example, mineral acids (e.g., hydrochloric acid, sulfuric acid and the like); Lewis acids (e.g., boron trichloride, boron tribromide and the like);

organic acids (e.g., trifluoroacetic acid, p-toluenesulfonic acid and the like), and the like can be mentioned. Lewis acid can be used concurrently with thiol or sulfide.

As the base, for example, alkali metal hydroxides (e.g., sodium hydroxide, potassium hydroxide, barium hydroxide and the like); alkali metal carbonates (e.g., sodium carbonate, potassium carbonate and the like); alkali metal alkoxides having 1 to 6 carbon atoms (e.g., sodium methoxide, sodium ethoxide, potassium tert-butoxide and the like); organic bases (e.g., triethylamine, imidazole, formamidine and the like), and the like can be mentioned. The amount of the acid and base to be used is about 0.5 to 10 mol, preferably about 0.5 to 6 mol, relative to 1 mol of compound (Ia').

The hydrolysis reaction is carried out without solvent, or using a solvent inert to the reaction. While the solvent is not particularly limited as long as the reaction proceeds, for example, solvents such as alcohols (e.g., methanol, ethanol, propanol and the like); aromatic hydrocarbons (e.g., benzene, toluene and the like); saturated hydrocarbons (e.g., cyclohexane, hexane and the like); organic acids (e.g., formic acid, acetic acid and the like); ethers (e.g., tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like); amides (e.g., N,N-dimethylformamide, N,N-dimethylacetamide and the like); halogenated hydrocarbons (e.g., dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like); nitriles (e.g., acetonitrile, propionitrile and the like); ketones (e.g., acetone, methyl ethyl ketone and the like); sulfoxides (e.g., dimethyl sulfoxide and the like); water and the like, a mixed solvent thereof and the like are preferable.

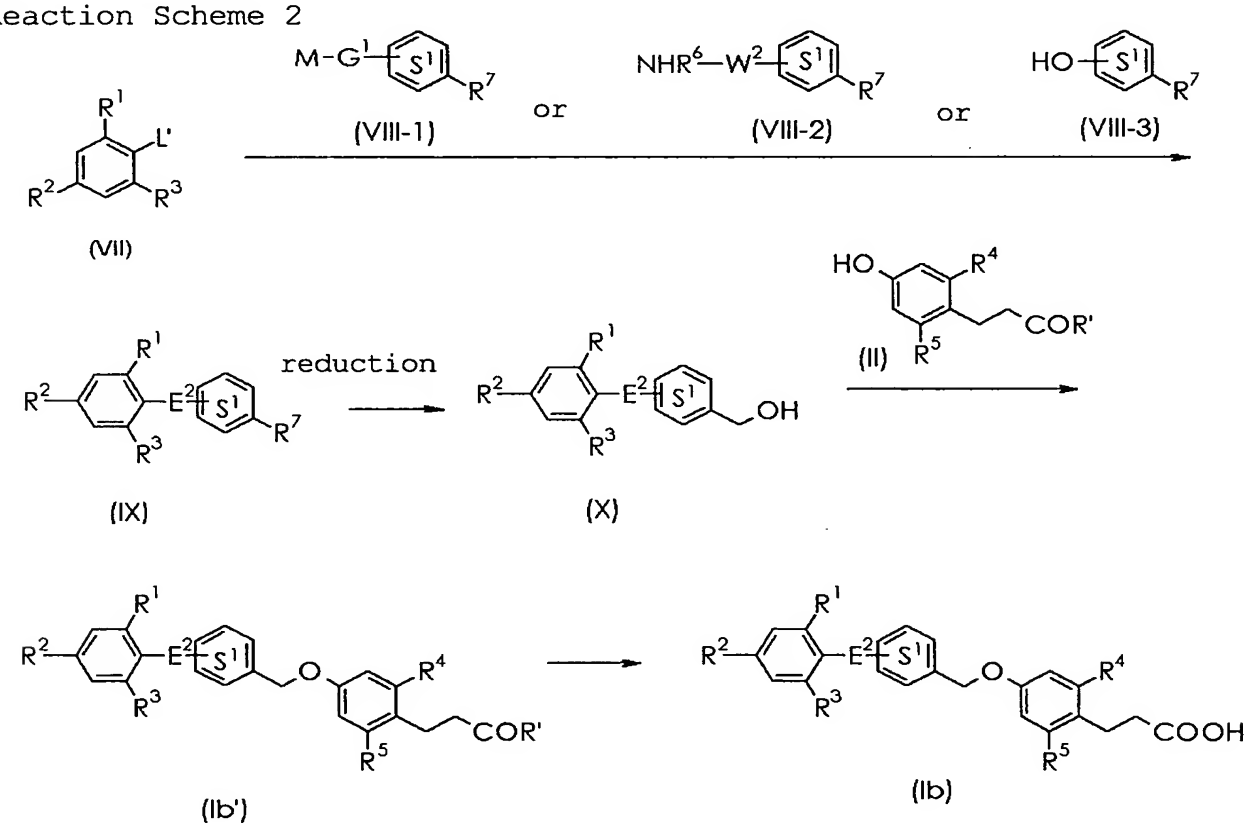
The reaction time is generally 10 min. to 60 hrs., preferably 10 min. to 12 hrs. The reaction temperature is generally -10 to 200°C, preferably 0 to 120°C.

Compound (I) wherein E is E^2 (E^2 is G^1 (G^1 is as defined above), $-N(R^6)-W^2-$ (R^6 and W^2 are as defined above) or -O-)

(compound represented by the formula (Ib') or (Ib) (to be abbreviated as compound (Ib') and compound (Ib))), can be produced, for example, according to the method shown by the following Reaction Scheme 2 or a method analogous thereto.

The compounds represented by the formula (VII), (VIII-1), (VIII-2) and (VIII-3) (to be abbreviated as compound (VII), compound (VIII-1), compound (VIII-2) and compound (VIII-3), respectively) are commercially easily available, and can be also produced according to a method known *per se* or a method analogous thereto.

Reaction Scheme 2



wherein R^7 is an optionally substituted C_{1-4} alkoxy-carbonyl group or a formyl group, the other symbols are as defined above.
As the "optionally substituted C_{1-4} alkoxy-carbonyl group" for R^7, C_{1-4} alkoxy-carbonyl group optionally having 1 to 3 substituent(s) such as phenyl group, halogen atom, C_{1-6} alkoxy group and the like (e.g., methoxycarbonyl, ethoxycarbonyl,

benzyloxycarbonyl, 2-(ethoxy)ethoxycarbonyl) and the like can be mentioned.

A compound represented by the formula (IX) (to be abbreviated as compound (IX)) can be produced by reacting compound (VII) with compound (VIII-1) or compound (VIII-2) or compound (VIII-3) (unless otherwise specified, these are collectively referred to as compound (VIII)) in the same manner as in the reaction of compound (IV) with compound (V) in the Reaction Scheme 1.

A compound represented by the formula (X) (to be abbreviated as compound (X)) can be produced by subjecting compound (IX) to reduction reaction.

The reduction reaction is carried out using a reduction agent according to a conventional method. As the reduction agent, for example, metal hydrides (e.g., aluminum hydride, diisobutylaluminum hydride, tributyltin hydride and the like); metal hydride complexes (e.g., lithium aluminum hydride, sodium borohydride and the like); borane complexes (e.g., borane tetrahydrofuran complex, borane dimethylsulfide complex and the like); alkyl boranes (e.g., thexylborane, disiamylborane and the like); diborane; metals (e.g., zinc, aluminum, tin, iron and the like); alkali metals (e.g., sodium, lithium and the like)/liquid ammonia (Birch reduction) and the like can be mentioned. The amount of the reduction agent to be used is appropriately determined according to the kind of the reduction agent. For example, the amount of the metal hydride or metal hydride complex to be used is about 0.25 to about 10 mol, preferably about 0.5 to about 5 mol, relative to 1 mol of compound (IX), the amount of the borane complex, alkyl boran or diborane to be used is about 1 to about 10 mol, preferably about 1 to about 5 mol, relative to 1 mol of compound (IX), and the amount of the metal (containing alkali metal used for Birch reduction) to be used is about 1 to about 20 equivalents, preferably about 1 to about 5 equivalents, relative to 1 equivalent of compound (IX).

The reduction reaction is advantageously carried out using a solvent inert to the reaction. While the solvent is not particularly limited as long as the reaction proceeds, for example, solvents such as alcohols (e.g., methanol, ethanol, 1-propanol, 2-propanol, tert-butyl alcohol and the like); ethers (e.g., diethyl ether, diisopropyl ether, diphenyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like); aromatic hydrocarbons (e.g., benzene, toluene and the like); saturated hydrocarbons (e.g., cyclohexane, hexane and the like); amides (e.g., N,N-dimethylformamide, N,N-dimethylacetamide, hexamethylphosphoric triamide and the like); organic acids (e.g., formic acid, acetic acid, propionic acid, trifluoroacetic acid, methanesulfonic acid and the like), and the like, a mixed solvent thereof and the like are preferable.

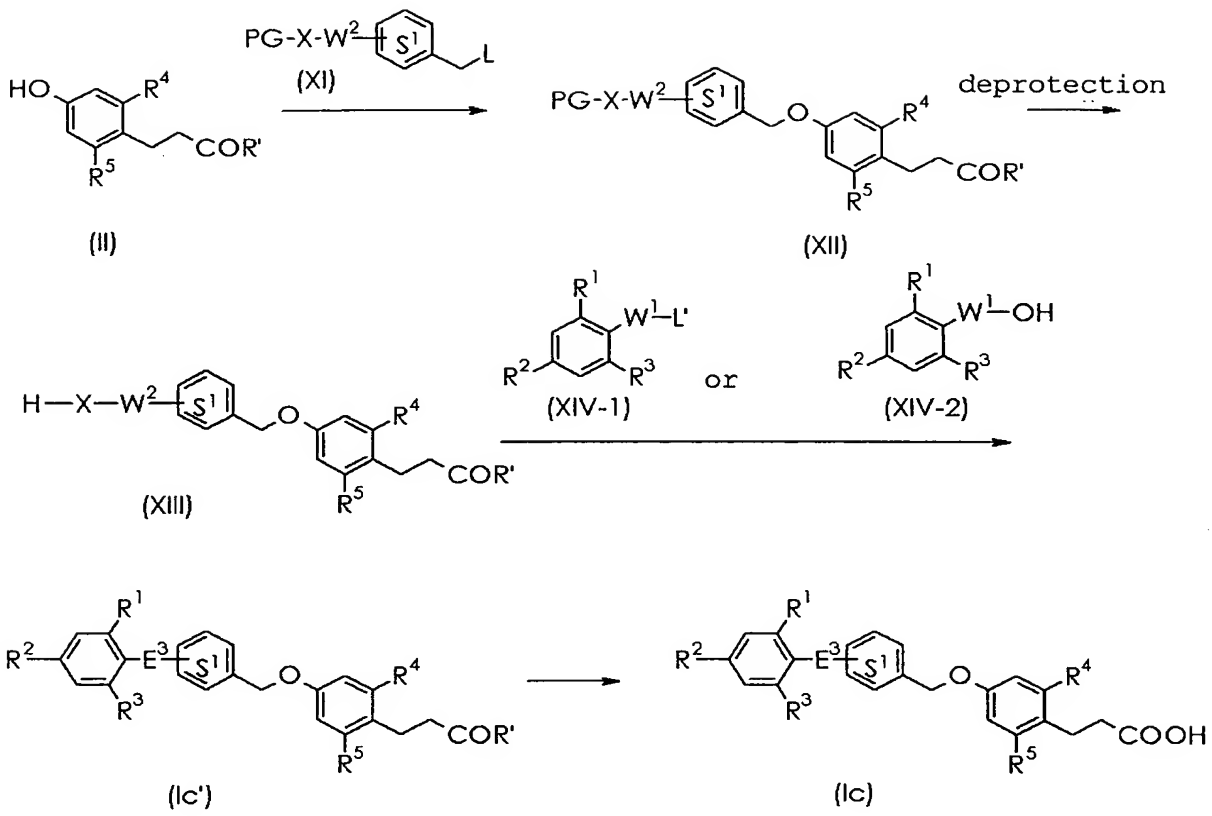
While the reaction time varies depending on the kind and amount of the reducing agent or the activity and amount of the catalyst, it is generally about 1 hr to about 100 hrs., preferably about 1 hr to about 50 hrs. The reaction temperature is generally about -20 to about 120°C, preferably about 0 to about 80°C.

Compound (Ib') can be produced by reacting compound (II) and compound (X) according to a method similar to Mitsunobu reaction of compound (II) with compound (III) in the Reaction Scheme 1.

Compound (Ib) can be produced from compound (Ib') according to a method similar to the hydrolysis reaction of compound (Ia') in the Reaction Scheme 1.

Compound (I) wherein E is E^3 (E^3 is $-W^1-O-W^2-$, $-W^1-S-W^2-$ or $-W^1-N(R^6)-W^2-$ (W^1, W^2 and R^6 are as defined above)), (compounds represented by the formula (Ic') and (Ic) (to be abbreviated as compound (Ic') and compound (Ic), respectively)), can be produced, for example, according to the method shown by the following Reaction Scheme 3 or a method analogous thereto.

Reaction Scheme 3



wherein PG is a protecting group, X is -O-, -S- or -N(R^6)- (R^6 is as defined above), and other symbols are as defined above.

As the protecting group for PG, the hydroxy-protecting group, amino-protecting group and mercapto-protecting group to be mentioned later can be used.

Compounds represented by the formula (XI), (XIV-1) and (XIV-2) (to be abbreviated as compound (XI), compound (XIV-1) and compound (XIV-2), respectively) are commercially easily available, and can be also produced according to a method known *per se* or a method analogous thereto.

A compound represented by the formula (XII) (to be abbreviated as compound (XII)) can be produced by reacting compound (II) with compound (XI) according to a method similar to the reaction of compound (II) with compound (III) in the Reaction Scheme 1.

A compound represented by the formula (XIII) (to be

abbreviated as compound (XIII)) can be produced by deprotecting compound (XII) according to a deprotection reaction known *per se* or a method analogous thereto.

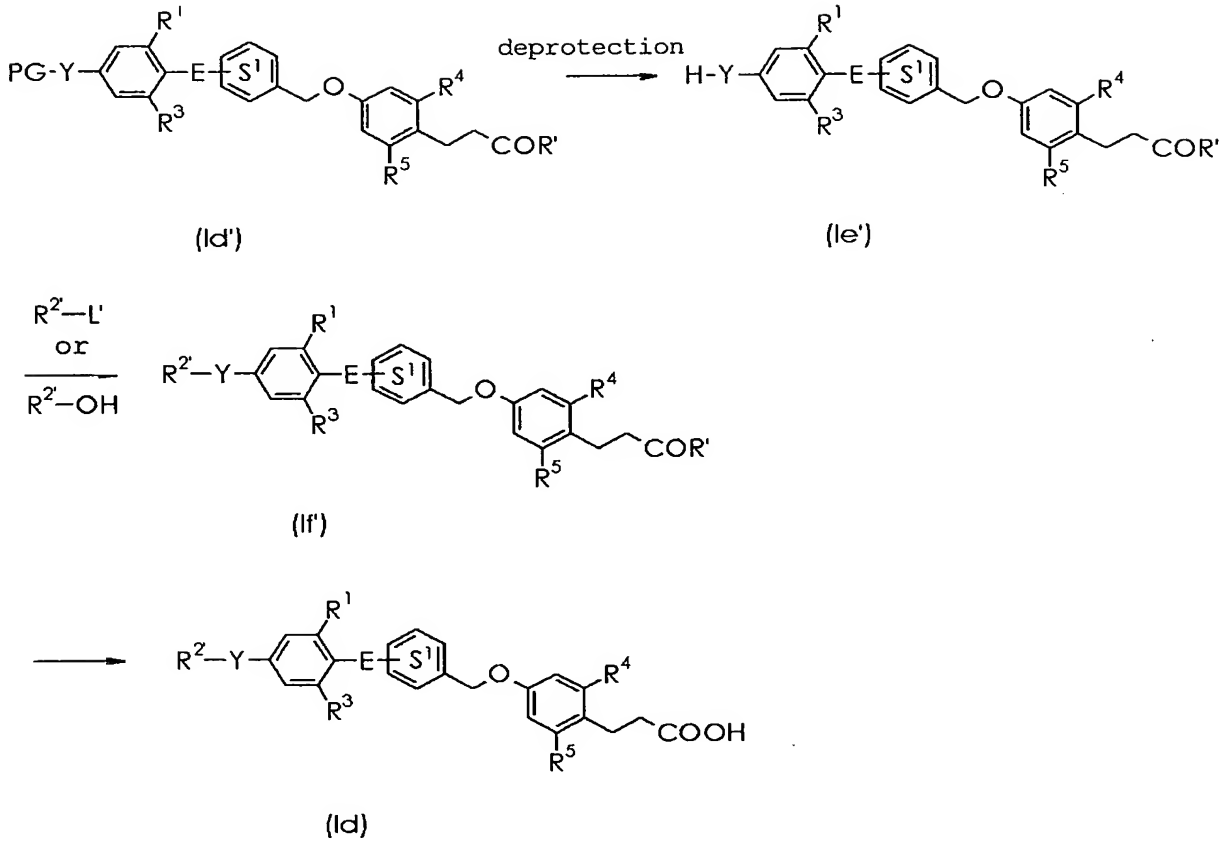
Compound (Ic') wherein E^3 is $-W^1-O-W^2-$, $-W^1-S-W^2-$ or $-W^1-N(R^6)-W^2-$, W^2 and R^6 are as defined above, and W^1 is an optionally substituted C_{1-3} alkylene group can be produced by reacting compound (XIII) with compound (XIV-1) according to a method similar to the reaction of compound (II) with compound (III) wherein L is a leaving group in the Reaction Scheme 1.

Compound (Ic') wherein E^3 is $-W^1-O-W^2-$ or $-W^1-S-W^2-$, and at least one of W^1 and W^2 is a bond can be also produced by reacting compound (XIII) wherein X is -O- or -S- with compound (XIV-2) according to a method similar to the reaction of Mitsunobu reaction of compound (II) with compound (III) in the Reaction Scheme 1.

Compound (Ic) can be produced from compound (Ic') according to a method similar to the hydrolysis reaction of compound (Ia') in the Reaction Scheme 1.

Compound (I) wherein R^2 is a substituted hydroxy group, a substituted amino group or a substituted mercapto group, namely, compound (I) wherein R^2 is $R^{2'}-Y-$ [Y is -O-, -S- or $-N(R^A)-$ (R^A is a hydrogen atom or a substituent possessed by the amino group of the "optionally substituted amino group" for R^2), and $R^{2'}$ is, when Y is -O-, a substituent possessed by the hydroxy group of the "optionally substituted hydroxy group" for R^2, when Y is -S-, a substituent possessed by the mercapto group of the "optionally substituted mercapto group" for R^2, when Y is $-N(R^A)-$, a substituent possessed by the amino group of the "optionally substituted amino group" for R^2)], (compounds represented by the formula (If') and (Id) (to be abbreviated as compound (If') and compound (Id), respectively)), can be produced, for example, according to the method shown by the following Reaction Scheme 4 or a method analogous thereto.

Reaction Scheme



wherein each symbol is as defined above.

A compound represented by the formula (Id') (to be abbreviated as compound (Id')) can be produced according to a method similar to the aforementioned compound (Ia'), compound (Ib') or compound (Ic').

A compound represented by the formula (Ie') (to be abbreviated as compound (Ie')) can be produced by subjecting compound (Id') to a deprotection reaction known *per se*.

Compound (If') can be produced by reacting compound (Ie') with a compound represented by the formula: $R^{2'}$-L', according to a method similar to the reaction of compound (II) with compound (III) wherein L is a leaving group in the Reaction Scheme 1.

Compound (If') wherein Y is -O- or -S- can be also produced by reacting compound (Ie') wherein Y is -O- or -S- with a compound represented by the formula: $R^{2'}$-OH according to a

method similar to Mitsunobu reaction of compound (II) with compound (III) in the Reaction Scheme 1.

Compound (Id) can be produced from compound (If') according to a method similar to the hydrolysis reaction of compound (Ia') in the Reaction Scheme 1.

In each of the aforementioned reactions, when the starting compound has amino group, carboxyl group, hydroxy group or mercapto group as a substituent, a protecting group generally used in peptide chemistry and the like may be introduced into these groups. By removing the protecting group as necessary after the reaction, the objective compound can be obtained.

As the amino-protecting group, for example, formyl, C_{1-6} alkyl-carbonyl (e.g., acetyl, ethylcarbonyl and the like), phenylcarbonyl, C_{1-6} alkyl-oxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl (Boc) and the like), allyloxycarbonyl (Aloc) group, phenyloxycarbonyl, fluorenylmethyloxycarbonyl (Fmoc), C_{7-10} aralkyl-carbonyl (e.g., benzylcarbonyl and the like), C_{7-10} aralkyl-oxycarbonyl (e.g., benzyloxycarbonyl (Z) and the like), C_{7-10} aralkyl (e.g., benzyl and the like), trityl, phthaloyl, dithiasuccinoyl or N,N-dimethylaminomethylene, which optionally has substituent(s), can be mentioned. As the substituent, phenyl group, halogen atom (e.g., fluorine, chlorine, bromine, iodine and the like), C_{1-6} alkyl-carbonyl group (e.g., methylcarbonyl, ethylcarbonyl, butylcarbonyl and the like), C_{1-6} alkoxy group (e.g., methoxy, ethoxy, trifluoromethoxy and the like) optionally substituted by a halogen atom (e.g., fluorine, chlorine, bromine, iodine and the like), nitro group and the like can be used. The number of the substituent is about 1 to 3.

As the carboxy-protecting group, for example, C_{1-6} alkyl (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl and the like), allyl, benzyl, phenyl, trityl or trialkylsilyl and the like, which optionally has substituent(s), can be mentioned. As the substituent, halogen atom (e.g., fluorine,

chlorine, bromine, iodine and the like), formyl, C_{1-6} alkyl-carbonyl (e.g., acetyl, ethylcarbonyl, butylcarbonyl and the like), C_{1-6} alkoxy group (e.g., methoxy, ethoxy, trifluoromethoxy and the like) optionally substituted by a halogen atom (e.g., fluorine, chlorine, bromine, iodine and the like), nitro group and the like can be used. The number of the substituent is about 1 to 3.

As the hydroxy-protecting group, for example, C_{1-6} alkyl (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl and the like), C_{7-10} aralkyl (e.g., benzyl and the like), formyl, C_{1-6} alkyl-carbonyl (e.g., acetyl, ethylcarbonyl and the like), benzoyl, C_{7-10} aralkyl-carbonyl (e.g., benzylcarbonyl and the like), tetrahydropyranyl, furanyl or silyl (e.g., trimethylsilyl, tert-butyldimethylsilyl, diisopropylethylsilyl and the like) and the like, which optionally has substituent(s), can be mentioned. As the substituent, halogen atom (e.g., fluorine, chlorine, bromine, iodine and the like), C_{1-6} alkyl (e.g., methyl, ethyl, n-propyl and the like), phenyl, C_{7-10} aralkyl (e.g., benzyl and the like), C_{1-6} alkoxy (e.g., methoxy, ethoxy, propoxy and the like), nitro group and the like can be used. The number of the substituent is about 1 to 4.

As the mercapto-protecting group, for example, C_{1-6} alkyl (e.g., tert-butyl and the like), C_{7-20} aralkyl (e.g., benzyl, trityl and the like) and the like, which optionally has substituent(s), can be mentioned. As the substituent, halogen atom (e.g., fluorine, chlorine, bromine, iodine and the like), C_{1-6} alkyl (e.g., methyl, ethyl, n-propyl and the like), phenyl, C_{7-10} aralkyl (e.g., benzyl and the like), C_{1-6} alkoxy (e.g., methoxy, ethoxy, n-propoxy and the like), nitro group and the like can be used. The number of the substituent is about 1 to 4.

For elimination of the protecting group, a method known *per se* or a method analogous thereto is used. For example, treatment with acid, base, reduction, ultraviolet rays, hydrazine, phenylhydrazine, sodium N-methyldithiocarbamate,

tetrabutylammonium fluoride, palladium acetate and the like are used.

Compound (I) obtained in this manner, other reaction intermediates and starting material compounds thereof can be isolated or purified from the reaction mixture by a method known *per se*, such as extraction, concentration, neutralization, filtration, distillation, recrystallization, column chromatography, thin layer chromatography, preparative high pressure liquid chromatography (preparative HPLC), intermediate pressure preparative liquid chromatography (intermediate pressure preparative LC) and the like.

The salt of compound (I) can be produced according to a method known *per se*. For example, when compound (I) is a basic compound, the salt can be produced by adding an inorganic acid or an organic acid, or when compound (I) is an acidic compound, by adding an organic base or an inorganic base.

When compound (I) has optical isomers, these respective optical isomers and mixtures thereof are naturally encompassed in the scope of the present invention, and where desired, these isomers can be also subjected to optical resolution or individually produced according to a method known *per se*.

When compound (I) is present as a configurational isomer (stereoisomer), diastereomer, conformer or the like, each can be isolated by the above separation and purification methods on demand. In addition, when compound (I) is in the form of racemates, they can be separated into S- and R-forms by any conventional optical resolution.

When compound (I) includes stereoisomers, both the isomers alone and mixtures of each isomers are included in the scope of the present invention.

In addition, compound (I) may be a hydrate or non-hydrate.

Compound (I) may be labeled with an isotope (e.g., ^{3}H, ^{14}C, ^{35}S and the like) or the like.

Compound (I), a salt thereof and a prodrug thereof (hereinafter sometimes to be abbreviated as the compound of the present invention) show GPR40 receptor function modulating action (GPR40 receptor agonist activity and GPR40 receptor antagonist activity), particularly GPR40 receptor agonist activity, show low toxicity and a fewer side effects (e.g., acute toxicity, chronic toxicity, genotoxicity, developmental toxicity, cardiac toxicity, drug interaction, cancinogenicity). Therefore, they are useful as a safe GPR40 receptor function modulator, preferably GPR40 agonist.

A pharmaceutical agent containing the compound of the present invention shows a superior GPR40 receptor function modifying action in mammal (e.g., mouse, rat, hamster, rabbit, cat, dog, bovine, sheep, monkey, human etc.), and is useful as a modulator of physiological function in which GPR40 receptor is involved or an agent for the prophylaxis or treatment of disease state or disease in which GPR40 receptor is involved.

To be specific, the pharmaceutical agent containing the compound of the present invention is useful as an insulin secretion modulator (preferably insulin secretagogue), hypoglycemic drug and pancreatic β cell protector.

Moreover, the pharmaceutical agent containing the compound of the present invention is useful as an agent for the prophylaxis or treatment of diseases such as diabetes, impaired glucose tolerance, ketosis, acidosis, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, macular edema, hyperlipidemia, genital disorder, skin disease, arthropathy, osteopenia, arteriosclerosis, thrombotic disease, dyspepsia, memory and learning disorder, obesity, hypoglycemia, hypertension, edema, insulin resistance, unstable diabetes, fatty atrophy, insulin allergy, insulinoma, lipotoxicity, hyperinsulinemia, cancers and the like; particularly, diseases such as diabetes, impaired glucose tolerance, ketosis, acidosis, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy,

macular edema, hyperlipidemia, genital disorder, skin disease, arthropathy, osteopenia, arteriosclerosis, thrombotic disease, dyspepsia, memory and learning disorder and the like. Here, diabetes includes type 1 diabetes, type 2 diabetes and pregnancy diabetes can be mentioned. In addition, hyperlipidemia includes hypertriglyceridemia, hypercholesterolemia, hypoHDL-emia, postprandial hyperlipidemia and the like.

For diagnostic criteria of diabetes, Japan Diabetes Society reported new diagnostic criteria in 1999.

According to this report, diabetes is a condition showing any of a fasting blood glucose level (glucose concentration of intravenous plasma) of not less than 126 mg/dl, a 75 g oral glucose tolerance test (75 g OGTT) 2 h level (glucose concentration of intravenous plasma) of not less than 200 mg/dl, and a non-fasting blood glucose level (glucose concentration of intravenous plasma) of not less than 200 mg/dl. A condition not falling under the above-mentioned diabetes and different from "a condition showing a fasting blood glucose level (glucose concentration of intravenous plasma) of less than 110 mg/dl or a 75 g oral glucose tolerance test (75 g OGTT) 2 h level (glucose concentration of intravenous plasma) of less than 140 mg/dl" (normal type) is called a "borderline type".

In addition, ADA (American Diabetes Association) reported new diagnostic criteria of diabetes in 1997 and WHO in 1998.

According to these reports, diabetes is a condition showing a fasting blood glucose level (glucose concentration of intravenous plasma) of not less than 126 mg/dl and a 75 g oral glucose tolerance test 2 h level (glucose concentration of intravenous plasma) of not less than 200 mg/dl.

According to the above-mentioned reports, impaired glucose tolerance is a condition showing a fasting blood glucose level (glucose concentration of intravenous plasma) of less than 126 mg/dl and a 75 g oral glucose tolerance test 2 h level (glucose concentration of intravenous plasma) of not less than 140 mg/dl

and less than 200 mg/dl. According to the report of ADA, a condition showing a fasting blood glucose level (glucose concentration of intravenous plasma) of not less than 110 mg/dl and less than 126 mg/dl is called IFG (Impaired Fasting Glucose). According to the report of WHO, among the IFG (Impaired Fasting Glucose), a condition showing a 75 g oral glucose tolerance test 2 h level (glucose concentration of intravenous plasma) of less than 140 mg/dl is called IFG (Impaired Fasting Glycemia).

The compound of the present invention can be also used as an agent for the prophylaxis or treatment of diabetes, borderline type, impaired glucose tolerance, IFG (Impaired Fasting Glucose) and IFG (Impaired Fasting Glycemia), as determined according to the above-mentioned new diagnostic criteria. Moreover, the compound of the present invention can prevent progress of borderline type, impaired glucose tolerance, IFG (Impaired Fasting Glucose) or IFG (Impaired Fasting Glycemia) into diabetes.

The pharmaceutical agent comprising the compound of the present invention shows low toxicity and can be safely administered orally or parenterally (e.g., topical, rectal, intravenous administration etc.) in the form of the compound of the present invention as it is or after admixing with a pharmacologically acceptable carrier to give a pharmaceutical preparation according to a method known *per se* used for the general production method for pharmaceutical preparations.

The dosage form of the aforementioned pharmaceutical preparation is, for example, an oral agent such as tablets (inclusive of sublingual tablets and orally disintegrable tablets), capsules (inclusive of soft capsules and micro capsules), granules, powders, troches, syrups, emulsions, suspensions and the like; or a parenteral agent such as injections (e.g., subcutaneous injections, intravenous injections, intramuscular injections, intraperitoneal injections, drip infusions etc.), external agents (e.g., transdermal

preparations, ointments etc.), suppositories (e.g., rectal suppositories, vaginal suppositories etc.), pellets, nasal preparations, pulmonary preparations (inhalations), ophthalmic preparations and the like.

These agents may be controlled-release preparations such as rapid-release preparations and sustained-release preparations (e.g., sustained-release microcapsules).

The content of the compound of the present invention in a pharmaceutical preparation of the present invention is about 0.01 to about 100% by weight relative to the whole preparation. The dose of the compound of the present invention varies depending on administration subjects, administration route, diseases, condition and the like. When the compound is orally administered to an adult patient with diabetes (body weight about 60 kg), about 0.01 to about 30 mg/kg body weight per day, preferably about 0.1 to about 20 mg/kg body weight per day, more preferably about 1 to about 20 mg/kg body weight per day, which may be given at once or several portions a day.

Various organic or inorganic carriers conventionally used as materials for pharmaceutical preparations are used as a pharmacologically acceptable carrier, which are added as excipient, lubricant, binder and disintegrant for solid preparations; and solvent, dissolution aids, suspending agent, isotonicity agent, buffer and soothing agent and the like for liquid preparations. Where necessary, additive such as preservative, antioxidant, coloring agent, sweetening agent, adsorbing agent, wetting agent and the like can be used.

As the excipient, for example, lactose, sucrose, D-mannitol, starch, corn starch, crystalline cellulose, light silicic anhydride and the like can be mentioned.

As the lubricant, for example, magnesium stearate, calcium stearate, talc, colloidal silica and the like can be mentioned.

As the binder, for example, crystalline cellulose, sucrose, D-mannitol, dextrin, hydroxypropylcellulose,

hydroxypropylmethylcellulose, polyvinylpyrrolidone, starch, sucrose, gelatin, methylcellulose, carboxymethylcellulose sodium and the like can be mentioned.

As the disintegrant, for example, starch, carboxymethylcellulose, carboxymethylcellulose calcium, carboxymethylstarch sodium, L-hydroxypropylcellulose and the like can be mentioned.

As the solvent, for example, water for injection, alcohol, propyleneglycol, macrogol, sesame oil, corn oil, olive oil and the like can be mentioned.

As the dissolution aids, for example, polyethylene glycol, propyleneglycol, D-mannitol, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate and the like can be mentioned.

As the suspending agent, for example, surfactants such as stearyltriethanolamine, sodium lauryl sulfate, lauryl aminopropionate, lecithin, benzalkonium chloride, benzethonium chloride, glycerol monostearate and the like; hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, carboxymethylcellulose sodium, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and the like, and the like can be mentioned.

As an isotonicity agent, for example, glucose, D-sorbitol, sodium chloride, glycerin, D-mannitol and the like can be mentioned.

As the buffer, for example, buffers such as phosphate, acetate, carbonate, citrate and the like, and the like can be mentioned.

As the soothing agent, for example, benzyl alcohol and the like can be mentioned.

As the preservative, for example, p-hydroxybenzoates, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid, sorbic acid and the like can be mentioned.

As the antioxidant, for example, sulfite, ascorbic acid, α-tocopherol and the like can be mentioned.

As the coloring agent, for example, water-soluble edible tar pigments (e.g., foodcolors such as Food Color Red Nos. 2 and 3, Food Color Yellow Nos. 4 and 5, Food Color Blue Nos. 1 and 2 and the like), water insoluble lake pigments (e.g., aluminum salt of the aforementioned water-soluble edible tar pigment and the like), natural pigments (e.g., β-carotene, chlorophil, red iron oxide etc.) and the like can be mentioned.

As the sweetening agent, for example, saccharin sodium, dipotassium glycyrrhizinate, aspartame, stevia and the like can be mentioned.

The compound of the present invention can be used in combination with drugs such as a therapeutic agent of diabetes, a therapeutic agent of diabetic complications, a therapeutic agent of hyperlipidemia, an antihypertensive agent, an antiobestic agent, a diuretic, a chemotherapeutic agent, an immunotherapeutic agent, an antiinflammatory drug, an antithrombotic agent, a therapeutic agent of osteoporosis, a vitamin, an antidementia agent, a therapeutic agent for incontinentia or pollakiuria, a therapeutic agent for dysurea and the like (hereinafter to be referred to as drug X).

As the therapeutic agent for diabetes, insulin preparations (e.g., animal insulin preparations extracted from the pancreas of bovine and pig; human insulin preparations genetically synthesized using *Escherichia coli*, yeast; zinc insulin; protamine zinc insulin; fragment or derivative of insulin (e.g., INS-1 etc.), oral insulin preparation and the like), insulin sensitizers (e.g., Pioglitazone or a salt thereof (preferably hydrochloride), Rosiglitazone or a salt thereof (preferably maleate), Reglixane (JTT-501), Netoglitazone (MCC-555), GI-262570, FK-614, CS-011, compounds described in WO99/58510 (e.g., (E)-4-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)benzyloxyimino]-4-phenylbutyric acid), compounds

described in WO01/38325, Tesaglitazar (AZ-242), BM-13-1258, LM-4156, MBX-102, LY-519818, MX-6054, LY-510929, Balaglitazone (NN-2344), T-131 or a salt thereof, THR-0921 etc.), α-glucosidase inhibitors (e.g., voglibose, acarbose, miglitol, emiglitate etc.), biguanides (e.g., phenformin, metformin, buformin or salts thereof (e.g., hydrochloride, fumarate, succinate) etc.), insulin secretagogues [sulfonylurea (e.g., tolbutamide, glibenclamide, gliclazide, chlorpropamide, tolazamide, acetohexamide, glyclopyramide, glimepiride etc.), repaglinide, senaglinide, mitiglinide or calcium salt hydrate thereof, nateglinide, etc.], GLP-1 receptor agonists [e.g., GLP-1, GLP-1MR agent, NN-2211, AC-2993 (exendin-4), BIM-51077, Aib(8,35)hGLP-1(7,37)NH_2, CJC-1131 etc.], dipeptidyl peptidase IV inhibitor (e.g., NVP-DPP-278, PT-100, P32/98, P93/01, NVP-DPP-728, LAF237, TS-021 etc.), β3 agonist (e.g., CL-316243, SR-58611-A, UL-TG-307, AJ-9677, AZ40140 etc.), amylin agonists (e.g., pramlintide etc.), phosphotyrosine phosphatase inhibitors (e.g., sodium vanadate etc.), gluconeogenesis inhibitors (e.g., glycogen phosphorylase inhibitor, glucose-6-phosphatase inhibitor, glucagon antagonist etc.), SGLT (sodium-glucose cotransporter) inhibitors (e.g., T-1095 etc.), 11β-hydroxysteroid dehydrogenase inhibitors (e.g., BVT-3498 etc.), adiponectin or agonist thereof, IKK inhibitors (e.g., AS-2868 etc.), leptin resistance improving drugs, somatostatin receptor agonists (compounds described in WO01/25228, WO03/42204, WO98/44921, WO98/45285, WO99/22735 etc.), glucokinase activators (e.g., Ro-28-1675) and the like can be mentioned.

Examples of the therapeutic agent for diabetic complications include aldose reductase inhibitors (e.g., Tolrestat, Epalrestat, Zenarestat, Zopolrestat, Fidarestat (SNK-860), AS-3201, Minalrestat (ARI-509), CT-112 etc.), neurotrophic factors and increasing drugs thereof (e.g., NGF, NT-3, BDNF, neurotrophin production-secretion promoters described in WO01/14372 (e.g., 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-

5-[3-(2-methylphenoxy)propyl]oxazole etc.) and the like), protein kinase C (PKC) inhibitors (e.g., LY-333531 etc.), AGE inhibitors (e.g., ALT-945, pimagedine, pyratoxanthine, N-phenacylthiazolium bromide (ALT-766), EXO-226, ALT-711, Pyridorin, Pyridoxamine etc.), active oxygen scavengers (e.g., thioctic acid etc.), cerebral vasodilators (e.g., tiopride etc.), somatostatin receptor agonists (BIM23190) and apoptosis signal regulating kinase-1 (ASK-1) inhibitors.

Examples of the therapeutic agent of hyperlipidemia include HMG-CoA reductase inhibitor (e.g., pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin, vitavastatin, rosuvastatin and salts thereof (e.g., sodium salt) etc.), squalene synthase inhibitors (e.g., compounds described in WO97/10224, such as N-[[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl]piperidine-4-acetic acid etc.), fibrate compounds (e.g., bezafibrate, clofibrate, simfibrate, clinofibrate etc.), antioxidant (e.g., lipoic acid, probucol) and the like.

Examples of the antihypertensive agent include angiotensin converting enzyme inhibitors (e.g., captopril, enalapril, delapril etc.), angiotensin II antagonists (e.g., losartan, candesartan cilexetil, eprosartan, valsartan, telmisartan, irbesartan, olmesartan medoxomil, tasosartan, 1-[[2'-(2,5-dihydro-5-oxo-4H-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl]-2-ethoxy-1H-benzimidazole-7-carboxylic acid etc.), calcium antagonists (e.g., manidipine, nifedipine, amlodipine, efonidipine, nicardipine etc.), Clonidine and the like.

Examples of the antiobestic agent include antiobestic agents acting on the central nervous system (e.g., Dexfenfluramine, fenfluramine, phentermine, Sibutramine, amfepramone, dexamphetamine, Mazindol, phenylpropanolamine, clobenzorex; MCH receptor antagonists (e.g., SB-568849; SNAP-7941; compounds encompassed in WO01/82925 and WO01/87834 etc.);

neuropeptide Y antagonists (e.g., CP-422935 etc.); cannabinoid receptor antagonists (e.g., SR-141716, SR-147778 etc.); ghrelin antagonist; 11β-hydroxysteroid dehydrogenase inhibitors (e.g., BVT-3498 etc.) and the like), pancreatic lipase inhibitors (e.g., orlistat, ATL-962 etc.), β3 agonists (e.g., CL-316243, SR-58611-A, UL-TG-307, AJ-9677, AZ40140 etc.), peptidic anorexiants (e.g., leptin, CNTF (Ciliary Neurotropic Factor) etc.), cholecystokinin agonists (e.g., lintitript, FPL-15849 etc.), feeding deterrent (e.g., P-57 etc.) and the like.

Examples of the diuretic include xanthine derivatives (e.g., sodium salicylate and theobromine, calcium salicylate and theobromine etc.), thiazide preparations (e.g., ethiazide, cyclopenthiazide, trichloromethyazide, hydrochlorothiazide, hydroflumethiazide, benzylhydrochlorothiazide, penflutizide, polythiazide, methyclothiazide etc.), antialdosterone preparations (e.g., spironolactone, triamterene etc.), carbonate dehydratase inhibitors (e.g., acetazolamide and the like), chlorobenzenesulfonamide preparations (e.g., chlortalidone, mefruside, indapamide etc.), azosemide, isosorbide, etacrynic acid, piretanide, bumetanide, furosemide and the like.

Examples of the chemotherapeutic agent include alkylation agents (e.g., cyclophosphamide, ifosfamide etc.), metabolic antagonists (e.g., methotrexate, 5-fluorouracil or its derivative, etc.), anti-cancer antibiotics (e.g., mitomycin, adriamycin etc.), plant-derived anti-cancer agents (e.g., vincristin, vindesine, taxol etc.), cisplatin, carboplatin, etopoxide and the like. Of these, furtulon and neofurtulon, which are 5-fluorouracil derivatives, and the like are preferable.

Examples of the immunotherapeutic agent include microorganism or bacterial components (e.g., muramyl dipeptide derivative, picibanil etc.), polysaccharides having immunity potentiating activity (e.g., lentinan, sizofiran, krestin etc.), cytokines obtained by genetic engineering techniques (e.g.,

interferon, interleukin (IL) etc.), colony stimulating factors (e.g., granulocyte colony stimulating factor, erythropoietin etc.) and the like, with preference given to interleukins such as IL-1, IL-2, IL-12 and the like.

As the antiinflammatory drug, for example, non-steroidal antiinflammatory agents such as aspirin, acetoaminofen, indomethacin and the like can be mentioned.

Examples of the antithrombotic agent include heparin (e.g., heparin sodium, heparin calcium, dalteparin sodium etc.), warfarin (e.g., warfarin potassium etc.), anti-thrombin drugs (e.g., aragatroban etc.), thrombolytic agents (e.g., urokinase, tisokinase, alteplase, nateplase, monteplase, pamiteplase etc.), platelet aggregation inhibitors (e.g., ticlopidine hydrochloride, cilostazol, ethyl icosapentate, beraprost sodium, sarpogrelate hydrochloride etc.) and the like.

Examples of the therapeutic agent of osteoporosis include alfacalcidol, calcitriol, elcatonin, calcitonin salmon, estriol, ipriflavone, pamidronate disodium, alendronate sodium hydrate, incadronate disodium and the like.

As the vitamin, for example, vitamin B_1, vitamin B_{12} and the like can be mentioned.

Examples of the antidementia agent include tacrine, donepezil, rivastigmine, galanthamine and the like.

Examples of the therapeutic agent for incontinentia or pollakiuria include flavoxate hydrochloride, oxybutynin hydrochloride, propiverine hydrochloride and the like.

Examples of the therapeutic agent for dysurea include acetylcholine esterase inhibitors (e.g., distigmine) and the like can be mentioned.

Furthermore, drugs having a cachexia-improving action established in animal models and clinical situations, such as cyclooxygenase inhibitors (e.g., Indometacin etc.), Progesterone derivatives (e.g., Megesterol acetate), glucosteroid (e.g., dexamethasone etc.), metoclopramide agents, tetrahydrocannabinol

agents, fat metabolism improving agents (e.g., eicosapentaenoic acid etc.), growth hormones, IGF-1, or antibodies to a cachexia-inducing factor such as TNF-α, LIF, IL-6, Oncostatin M and the like, can be used in combination with the compound of the present invention.

Further, glycosylation inhibitors (e.g., ALT-711, etc.), nerve regeneration promoting drugs (e.g., Y-128, VX853, prosaptide, etc.), antidepressants (e.g., desipramine, amitriptyline, imipramine, etc.), anticonvulsants (e.g., lamotrigine, Trileptal, Keppra, Zonegran, Pregabalin, Harkoseride, carbamazepine), antiarrhythmic drugs (e.g., mexiletine), acetylcholine receptor ligands (e.g., ABT-594), endothelin receptor antagonists (e.g., ABT-627), monoamine uptake inhibitors (e.g., tramadol), narcotic analgesics (e.g., morphine), GABA receptor agonists (e.g., gabapentin, gabapentin MR agent), α_2 receptor agonists (e.g., clonidine), local analgesics (e.g., capsaicin), antianxiety drugs (e.g., benzothiazepines), phosphodiesterase inhibitors (e.g., sildenafil), dopamine receptor agonists (e.g., apomorphine) and the like can be also used in combination with the compound of the present invention.

Two or more kinds of the above-mentioned drug X may be used in an appropriate combination.

By combining the compound of the present invention and a drug X, a superior effect such as

(1) the dose of the compound of the present invention or a drug X can be reduced as compared to single administration of the compound of the present invention or a drug X,

(2) the period of treatment can be set longer by selecting a drug X having different action and mechanism from those of the compound of the present invention,

(3) a sustained treatment effect can be designed by selecting a drug X having different action and mechanism from those of the compound of the present invention,

(4) a synergistic effect can be afforded by a combined use of the compound of the present invention and a drug X, and the like, can be achieved.

When the compound of the present invention and a drug X are used in combination, the administration time of the compound of the present invention and the drug X is not restricted, and the compound of the present invention and the drug X can be administered to an administration subject simultaneously, or may be administered at staggered times. The dosage of the drug X may be determined according to the dose clinically used, and can be appropriately selected depending on an administration subject, administration route, disease, combination and the like.

The administration mode of the compound of the present invention and drug X is not particularly restricted, as long as the compound of the present invention and the drug X are combined in administration. Examples of such administration mode include the following methods: (1) The compound of the present invention and the drug X are simultaneously formulated to give a single preparation which is administered. (2) The compound of the present invention and the drug X are separately formulated to give two kinds of preparations which are administered simultaneously by the same administration route. (3) The compound of the present invention and the drug X are separately formulated to give two kinds of preparations which are administered by the same administration route at staggered times. (4) The compound of the present invention and the drug X are separately formulated to give two kinds of preparations which are administered simultaneously by the different administration routes. (5) The compound of the present invention and the drug X are separately formulated to give two kinds of preparations which are administered by the different administration routes at staggered times (for example, the compound of the present invention and the drug X are

administered in this order, or in the reverse order), and the like.

【Examples】

The present invention is further explained in detail by referring to the following Reference Examples, Examples, Formulation Examples and Experimental Example, which are mere working examples not to be construed as limitative and may be changed without departing from the scope of the present invention.

The term "room temperature" in the following Reference Examples and Examples indicates the range of generally from about 10°C to about 35°C. As for "%", the yield is in mol/mol%, the solvent used for chromatography is in % by volume and other "%" is in % by weight. OH proton, NH proton etc. that could not be confirmed due to broad peak by proton NMR spectrum are not included in the data.

The other symbols used herein mean the following:

s : singlet

d : doublet

t : triplet

q : quartet

m : multiplet

br : broad

J : coupling constant

Hz : Hertz

$CDCl_3$: deuterated chloroform

^1H NMR : proton nuclear magnetic resonance

In the following Reference Examples and Examples, mass spectrum (MS) and nuclear magnetic resonance spectrum (NMR) were measured under the following conditions.

MS measurement tools: Waters Corporation ZMD, Waters Corporation ZQ2000 or Micromass Ltd., platform II.

ionization method: Electron Spray Ionization (ESI) or Atmospheric Pressure Chemical Ionization (APCI). Unless specifically indicated, ESI was used.

NMR measurement tools: Varian Gemini 200 (200 MHz), Varian Gemini 300 (300 MHz), Varian, AVANCE 300, Bruker BioSpin Corp.

In Reference Examples and Examples, purification by preparative HPLC was performed under the following conditions.

preparative HPLC tools: Gilson, Inc., high through-put purification system

column: YMC Combiprep ODS-A S-5 μm, 20 X 50 mm

solvent:

Solution A; 0.1% trifluoroacetic acid-containing water,

Solution B; 0.1% trifluoroacetic acid-containing acetonitrile

gradient cycle A: 0.00 min (Solution A/Solution B= 90/10), 1.20 min (Solution A/Solution B= 90/10), 4.75 min (Solution A/Solution B= 0/100), 7.30 min (Solution A/Solution B= 0/100), 7.40 min (Solution A/Solution B= 90/10), 7.50 min (Solution A/Solution B= 90/10).

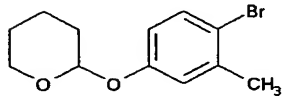
gradient cycle B: 0.00 min (Solution A/Solution B= 95/5), 1.00 min (Solution A/Solution B= 95/5), 5.20 min (Solution A/Solution B= 5/95), 6.40 min (Solution A/Solution B= 5/95), 6.50 min (Solution A/Solution B= 95/5), 6.60 min (Solution A/Solution B= 95/5).

flow rate: 25 ml/min,

detection method: UV 220 nm

Reference Example 1

2-(4-bromo-3-methylphenoxy)tetrahydro-2H-pyran



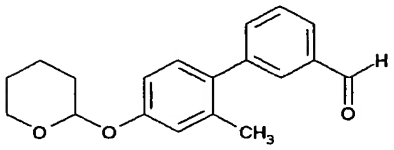
A solution of 4-bromo-3-methylphenol (4.72 g, 25.2 mmol), 3,4-dihydro-2H-pyran (3.18 g, 37.8 mmol) and pyridinium p-

toluenesulfonate (0.628 g, 2.50 mmol) in dichloromethane (100 mL) was stirred at room temperature for 24 hrs. The reaction mixture was washed with water, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to give the title compound (7.11 g, including unreacted 3,4-dihydro-2H-pyran) as a yellow oil.

^{1}H NMR ($CDCl_3$) δ:1.58-2.06(6H, m), 2.35(3H, s), 3.56-3.63(1H, m), 3.83-3.91(1H, m), 5.37(1H, t, J=3.1Hz), 6.77(1H, dd, J=8.8, 3.0Hz), 6.95(1H, d, J=3.0Hz), 7.39(1H, d, J=8.8Hz).

Reference Example 2

2'-methyl-4'-(tetrahydro-2H-pyran-2-yloxy)biphenyl-3-carbaldehyde



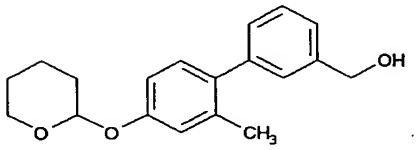
2-(4-Bromo-3-methylphenoxy)tetrahydro-2H-pyran (7.11 g, 25.2 mmol, including 3,4-dihydro-2H-pyran) and (3-formylphenyl)boronic acid (4.50 g, 30.0 mmol) were dissolved in a mixture of 1 M aqueous sodium carbonate solution (60 mL), ethanol (30 mL) and toluene (60 mL), and after argon substitution, tetrakis(triphenylphosphine)palladium(0) (1.73 g, 1.50 mmol) was added. The reaction mixture was stirred under an argon atmosphere at 80°C for 15 hrs. The reaction mixture was cooled, water and ethyl acetate were added, and insoluble material was filtered off through celite. The organic layer of the filtrate was washed with saturated brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (5%-30% ethyl acetate/hexane) to give the title compound (6.16 g, yield 82%, 2 steps) as a pale-yellow oil.

^{1}H NMR ($CDCl_3$) δ: 1.53-1.77(3H, m), 1.86-1.91(2H, m), 1.98-2.09(1H, m), 2.25(3H, s), 3.61-3.68(1H, m), 3.91-3.99(1H, m),

5.48(1H, t, J=3.2Hz), 6.95-7.00(2H, m), 7.15(1H, d, J=8.3Hz), 7.53-7.60(2H, m), 7.82-7.86(2H, m), 10.06(1H, s).

Reference Example 3

[2'-methyl-4'-(tetrahydro-2H-pyran-2-yloxy)biphenyl-3-yl]methanol

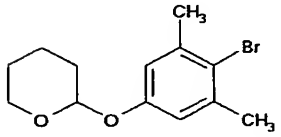


2'-Methyl-4'-(tetrahydro-2H-pyran-2-yloxy)biphenyl-3-carbaldehyde (13.6 g, 45.9 mmol) was dissolved in a mixture of 1,2-dimethoxyethane (70 mL) and tetrahydrofuran (70 mL), and sodium borohydride (0.870 g, 23.0 mmol) was added under ice-cooling. The mixture was stirred at the same temperature for 3 hrs. To the reaction mixture was added aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (15%-50% ethyl acetate/hexane) to give the title compound (12.2 g, yield 89%) as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 1.59-1.76(4H, m), 1.85-1.90(2H, m), 1.97-2.11(1H, m), 2.25(3H, s), 3.60-3.67(1H, m), 3.91-3.99(1H, m), 4.73(2H, d, J=5.8Hz), 5.46(1H, t, J=3.1Hz), 6.92-6.97(2H, m), 7.14(1H, d, J=8.1Hz), 7.22-7.41(4H, m).

Reference Example 4

2-(4-bromo-3,5-dimethylphenoxy)tetrahydro-2H-pyran

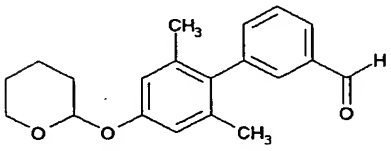


A solution of 4-bromo-3,5-dimethylphenol (10.5 g, 52.2 mmol), 3,4-dihydro-2H-pyran (8.83 g, 105 mmol) and pyridinium p-toluenesulfonate (2.64 g, 10.5 mmol) in dichloromethane (160 mL) was stirred at room temperature for 80 hrs. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (hexane-20% ethyl acetate/hexane) to give the title compound (11.5 g, yield 77%) as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 1.56-1.75(3H, m), 1.80-2.07(3H, m), 2.37(6H, s), 3.55-3.64(1H, m), 3.83-3.93(1H, m), 5.37(1H, t, J=3.1Hz), 6.80(2H, s).

Reference Example 5

2',6'-dimethyl-4'-(tetrahydro-2H-pyran-2-yloxy)biphenyl-3-carbaldehyde

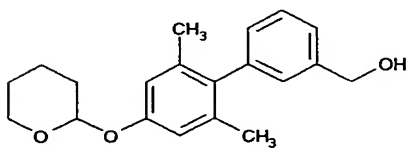


The title compound was obtained as a yellow oil from 2-(4-bromo-3,5-dimethylphenoxy)tetrahydro-2H-pyran and (3-formylphenyl)boronic acid according to a method similar to the method of Reference Example 2 (yield 83%).

^{1}H NMR ($CDCl_3$) δ: 1.57-1.78(3H, m), 1.82-1.93(2H, m), 1.99(6H, s), 2.04(1H, m), 3.65(1H, m), 3.97(1H, m), 5.47(1H, t, J=3.0Hz), 6.84(2H, s), 7.42(1H, m), 7.58(1H, t, J=7.5Hz), 7.67(1H, s), 7.86(1H, m), 10.05(1H, s).

Reference Example 6

[2',6'-dimethyl-4'-(tetrahydro-2H-pyran-2-yloxy)biphenyl-3-yl]methanol

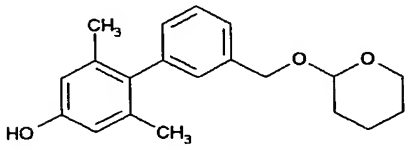


The title compound was obtained as a colorless oil from 2',6'-dimethyl-4'-(tetrahydro-2H-pyran-2-yloxy)biphenyl-3-carbaldehyde according to a method similar to the method of Reference Example 3 (yield 83%).

^{1}H NMR ($CDCl_3$) δ: 1.55-1.79(4H, m), 1.80-1.93(2H, m), 2.00(6H, s), 2.03(1H, m), 3.64(1H, m), 3.97(1H, m), 4.73(2H, d, J=5.7Hz), 5.45(1H, t, J=3.0Hz), 6.81(2H,s), 7.07(1H, d, J=7.5Hz), 7.13(1H, s), 7.33(1H, d, J=7.5Hz), 7.40(1H, t, J=7.8Hz).

Reference Example 7

2,6-dimethyl-3'-[(tetrahydro-2H-pyran-2-yloxy)methyl]biphenyl-4-ol

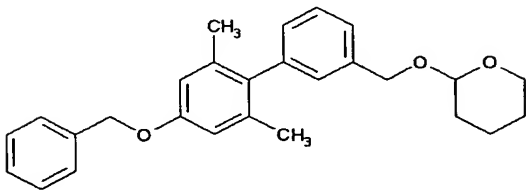


2',6'-Dimethyl-4'-(tetrahydro-2H-pyran-2-yloxy)biphenyl-3-carbaldehyde (9.05 g, 29.2 mmol) was dissolved in a mixture of 1,2-dimethoxyethane (50 mL) and tetrahydrofuran (50 mL), and sodium borohydride (0.567 g, 15.0 mmol) was added under ice-cooling. The mixture was stirred at the same temperature for 3 hrs. 10% Aqueous citric acid solution was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (15%-50% ethyl acetate/hexane) to give the title compound (3.24 g, yield 36%) as colorless crystals.

^{1}H NMR ($CDCl_3$) δ: 1.47-1.93(6H, m), 1.98(3H, s), 1.99(3H, s), 3.50-3.58(1H, m), 3.88-3.96(1H, m), 4.54(1H, d, J=12.1Hz), 4.68(1H, s), 4.73(1H, t, J=3.4Hz), 4.83(1H, d, J=12.1Hz), 6.59(2H, s), 7.04(1H, d, J=7.3Hz), 7.13(1H, s), 7.30-7.34(1H, m), 7.38(1H, t, J=7.3Hz).

Reference Example 8

2-{[4'-(benzyloxy)-2',6'-dimethylbiphenyl-3-yl]methoxy}tetrahydro-2H-pyran

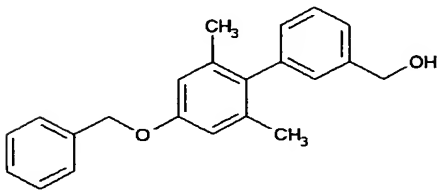


A solution of 2,6-dimethyl-3'-[(tetrahydro-2H-pyran-2-yloxy)methyl]biphenyl-4-ol (1.78 g, 5.70 mmol), benzyl alcohol (0.885 mL, 8.55 mmol) and tributylphosphine (2.13 mL, 8.55 mmol) in toluene (80 mL) was stirred under ice-cooling, and 1,1'-(azodicarbonyl)dipiperidine (2.16 g, 8.55 mmol) was added by small portions. The mixture was warmed to room temperature and stirred for 24 hrs. Hexane (40 mL) was added to the reaction mixture and the precipitated insoluble material was filtered off. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane-10% ethyl acetate/hexane) to give the title compound as a colorless oil (1.71 g, yield 75%).

^{1}H NMR ($CDCl_3$) δ: 1.47-1.93(6H, m), 2.01(3H, s), 2.02(3H, s), 3.50-3.57(1H, m), 3.88-3.96(1H, m), 4.54(1H, d, J=12.2Hz), 4.73(1H, t, J=3.5Hz), 4.83(1H, d, J=12.2Hz), 5.07(2H, s), 6.75(2H, s), 7.05(1H, d, J=7.2Hz), 7.14(1H, s), 7.30-7.48(7H, m).

Reference Example 9

[4'-(benzyloxy)-2',6'-dimethylbiphenyl-3-yl]methanol



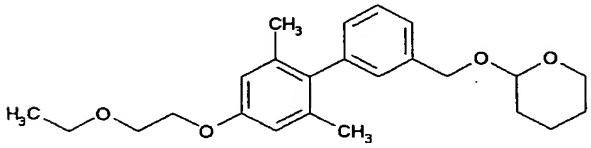
A solution of 2-{[4'-(benzyloxy)-2',6'-dimethylbiphenyl-3-yl]methoxy}tetrahydro-2H-pyran (1.71 g, 4.25 mmol) and p-

toluenesulfonic acid monohydrate (80.8 mg, 0.425 mmol) in methanol (15 mL) was stirred at room temperature for 20 hrs. The reaction solvent was evaporated under reduced pressure and the residue was diluted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (20%-50% ethyl acetate/hexane) to give the title compound (1.13 g, yield 84%) as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 1.65(1H, t, J=5.9Hz), 2.01(6H, s), 4.73(2H, d, J=5.9Hz), 5.07(2H, s), 6.75(2H, s), 7.07(1H, d, J=7.3Hz), 7.13(1H, s), 7.30-7.48(7H, m).

Reference Example 10

2-{[4'-(2-ethoxyethoxy)-2',6'-dimethylbiphenyl-3-yl]methoxy}tetrahydro-2H-pyran

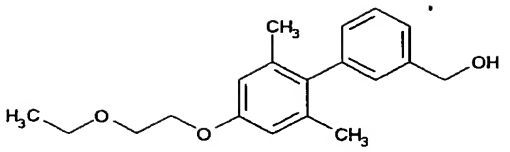


The title compound was obtained as a colorless oil from 2,6-dimethyl-3'-[(tetrahydro-2H-pyran-2-yloxy)methyl]biphenyl-4-ol and 2-ethoxyethanol according to a method similar to the method of Reference Example 8 (yield 74%).

^{1}H NMR ($CDCl_3$) δ: 1.25(3H, t, J=7.1Hz), 1.48-1.94(6H, m), 2.00(3H, s), 2.01(3H, s), 3.50-3.57(1H, m), 3.62(2H, q, J=7.1Hz), 3.80(2H, t, J=5.0Hz), 3.88-3.96(1H, m), 4.14(2H, t, J=5.0Hz), 4.54(1H, d, J=12.1Hz), 4.72(1H, t, J=3.5Hz), 4.82(1H, d, J=12.1Hz), 6.69(2H, s), 7.04(1H, d, J=7.3Hz), 7.13(1H, s), 7.32(1H, d, J=7.3Hz), 7.38(1H, t, J=7.3Hz).

Reference Example 11

[4'-(2-ethoxyethoxy)-2',6'-dimethylbiphenyl-3-yl]methanol

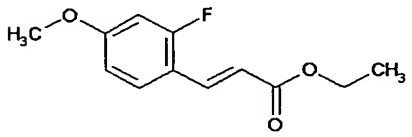


The title compound was obtained as a colorless oil from 2-{[4'-(2-ethoxyethoxy)-2',6'-dimethylbiphenyl-3-yl]methoxy}tetrahydro-2H-pyran according to a method similar to the method of Reference Example 9 (yield 82%).

MS m/z 301(MH^+)

Reference Example 12

ethyl (2E)-3-(2-fluoro-4-methoxyphenyl)acrylate

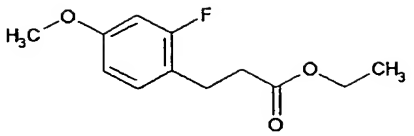


To an ice-cooled solution of ethyl diethylphosphonoacetate (9.45 g, 42.1 mmol) in tetrahydrofuran (50 mL) was added sodium hydride (60% oil suspension, 1.54 g, 38.5 mmol) and the mixture was stirred for 15 min. A solution of 2-fluoro-4-methoxybenzaldehyde (5.00 g, 32.4 mmol) in tetrahydrofuran (30 mL) was added dropwise. The mixture was stirred at room temperature for 2 hrs. and water was added. The mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (20% ethyl acetate/hexane) to give the title compound (7.07 g, yield 97%) as a colorless oil.

^1H NMR ($CDCl_3$) δ: 1.33(3H, t, J=7.1Hz), 3.83(3H, s), 4.26(2H, q, J=7.1Hz), 6.41(1H, d, J=16.2Hz), 6.61-6.73(2H, m), 7.45(1H, t, J=8.6Hz), 7.75(1H, d, J=16.2Hz).

Reference Example 13

ethyl 3-(2-fluoro-4-methoxyphenyl)propanoate

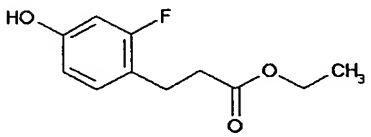


A mixture of ethyl (2E)-3-(2-fluoro-4-methoxyphenyl)acrylate (7.07 g, 31.5 mmol), tetrahydrofuran (50 mL), ethanol (5 mL) and platinum oxide (300 mg) was stirred overnight under a hydrogen atmosphere at room temperature. The catalyst was filtered off and the filtrate was concentrated. The residue was purified by silica gel column chromatography (20% ethyl acetate/hexane) to give the title compound (5.97 g, yield 84%) as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 1.23(3H, t, J=7.2Hz), 2.58(2H, t, J=7.6Hz), 2.90(2H, t, J=7.6Hz), 3.77(3H, s), 4.12(2H, q, J=7.2Hz), 6.57-6.63(2H, m), 7.07-7.13(1H, m).

Reference Example 14

ethyl 3-(2-fluoro-4-hydroxyphenyl)propanoate

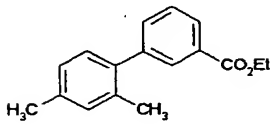


To a solution of ethyl 3-(2-fluoro-4-methoxyphenyl)propanoate (57.4 g, 254 mmol) and aluminum chloride (101 g, 761 mmol) in dichloromethane (250 mL) was added dropwise octanethiol (74.3 g, 508 mmol) and the mixture was stirred at room temperature for 2 hrs. The reaction mixture was poured into ice water and the mixture was stirred for 30 min. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (20% ethyl acetate/hexane) to give the title compound (44.6 g, yield 83%) as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 1.23(3H, t, J=7.2Hz), 2.58(2H, t, J=8.1Hz), 2.89(2H, t, J=8.1Hz), 4.12(2H, q, J=7.2Hz), 6.51-6.56(2H, m), 7.01-7.06(1H, m).

Reference Example 15

ethyl 2',4'-dimethylbiphenyl-3-carboxylate

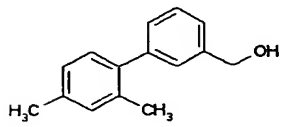


(2,4-Dimethylphenyl)boronic acid (3.0 g, 20.0 mmol), ethyl 3-bromobenzoate (4.3 g, 18.8 mmol) and cesium carbonate (9.8 g, 30.0 mmol) were added to a mixture of ethanol (20 mL) and toluene (80 mL), and after argon substitution, tetrakis(triphenylphosphine)palladium(0) (0.30 g, 0.26 mmol) was added. The reaction mixture was stirred under an argon atmosphere at 70°C for 18 hrs. The reaction mixture was cooled and insoluble material was filtered off through celite. The filtrate was concentrated under reduced pressure and the obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:10) to give the title compound (5.0 g) as a colorless oil (yield 100%).

^{1}H NMR ($CDCl_3$) δ:1.39(3H,t,J=7.0Hz), 2.23(3H,s), 2.37(3H,s), 4.38(2H,q,J=7.0Hz), 7.02-7.54(5H,m), 8.00-8.05(2H,m).

Reference Example 16

(2',4'-dimethylbiphenyl-3-yl)methanol



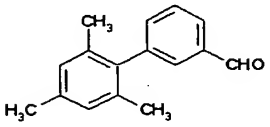
To a solution of ethyl 2',4'-dimethylbiphenyl-3-carboxylate (5.0 g, 19.7 mmol) in anhydrous tetrahydrofuran (50 mL) was added lithium aluminum hydride (0.91 g, 24.0 mmol) under

ice-cooling and the mixture was stirred at room temperature for 3 hrs. The reaction solution was ice-cooled and sodium sulfate 10 hydrate (8.0 g, 24.8 mmol) was added. The mixture was stirred at room temperature for 1 hr. The precipitated insoluble material was filtered off through celite, and the filtrate was concentrated under reduced pressure to give the title compound as a colorless oil (yield 96%).

^{1}H NMR ($CDCl_3$) δ:2.24(3H,s), 2.36(3H,s), 4.73(2H,d,J=6.0Hz), 7.00-7.45(7H,m).

Reference Example 17

2',4',6'-trimethylbiphenyl-3-carbaldehyde

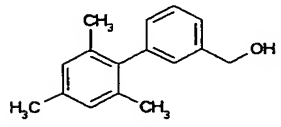


The title compound was obtained as a colorless oil from (2,4,6-trimethylphenyl)boronic acid and 3-bromobenzaldehyde according to a method similar to the method of Reference Example 15 (yield 76%).

MS m/z 225(MH^+)

Reference Example 18

(2',4',6'-trimethylbiphenyl-3-yl)methanol



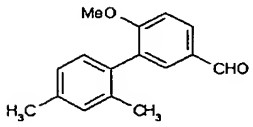
2',4',6'-Trimethylbiphenyl-3-carbaldehyde (2.36 g, 10.5 mmol) was dissolved in ethanol (20 mL), and sodium borohydride (0.40 g, 10.6 mmol) was added to the solution. After stirring under ice-cooling for 3 hrs., aqueous citric acid solution was added to the reaction solution. The mixture was extracted with ethyl acetate, washed with aqueous sodium chloride solution,

dried over magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:5-1:2) to give the title compound (1.66 g) as a colorless oil (yield 70%).

^{1}H NMR ($CDCl_3$) δ: 2.00(6H,s), 2.33(3H,s), 4.73(2H,d,J=6.2Hz), 6.94(2H,s), 7.00-7.42(4H,m).

Reference Example 19

6-methoxy-2',4'-dimethylbiphenyl-3-carbaldehyde

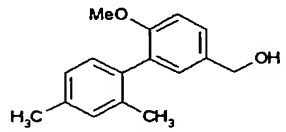


The title compound was obtained as a colorless oil from 1-bromo-2,4-dimethylbenzene and (5-formyl-2-methoxyphenyl)boronic acid according to a method similar to the method of Reference Example 15 (yield 87%).

MS m/z 241(MH^+)

Reference Example 20

(6-methoxy-2',4'-dimethylbiphenyl-3-yl)methanol

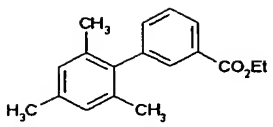


The title compound was obtained as a colorless oil from 6-methoxy-2',4'-dimethylbiphenyl-3-carbaldehyde according to a method similar to the method of Reference Example 18 (yield 88%).

^{1}H NMR ($CDCl_3$) δ: 2.01(6H,s), 3.74(3H,s), 4.65(2H,d,J=5.2Hz), 6.97(1H,d,J=8.4Hz), 7.03(1H,d,J=2.2Hz), 7.06-7.24(3H,m), 7.35(1H,dd,J=2.6 & 8.4Hz).

Reference Example 21

ethyl 2',4',6'-trimethylbiphenyl-3-carboxylate

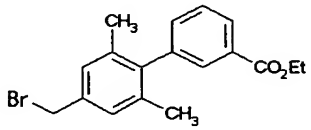
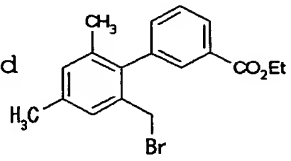


The title compound was obtained as a colorless oil from (2,4,6-trimethylphenyl)boronic acid and ethyl 3-bromobenzoate according to a method similar to the method of Reference Example 15 (yield 80%).

MS m/z 269(MH^+)

Reference Example 22

ethyl 4'-bromomethyl-2',6'-dimethylbiphenyl-3-carboxylate and ethyl 2'-bromomethyl-4',6'-dimethylbiphenyl-3-carboxylate

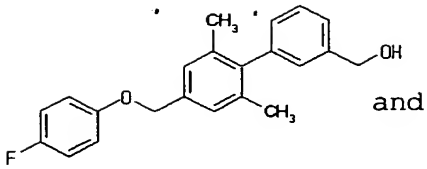
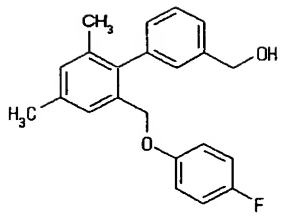
Mixture of  and 

A solution of ethyl 2',4',6'-trimethylbiphenyl-3-carboxylate (1.0 g, 3.73 mmol), N-bromosuccinimide (0.70 g, 3.93 mmol) and 2,2'-azobis(isobutyronitrile) (65 mg, 0.40 mmol) in carbon tetrachloride (30 mL) was stirred at 80°C for 5 hrs. The reaction solution was cooled to room temperature, and the precipitated insoluble material was filtered off. The filtrate was concentrated under reduced pressure, and the obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:10-1:5) to give a mixture (0.82 g) of the title compounds as a colorless oil. The mixture was used for the next reaction without separation (yield 64%).

MS m/z 348(MH^+)

Reference Example 23

[4'-[(4-fluorophenoxy)methyl]-2',6'-dimethylbiphenyl-3-yl]methanol and [2'-[(4-fluorophenoxy)methyl]-4',6'-dimethylbiphenyl-3-yl]methanol

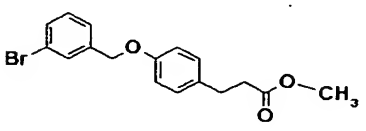
Mixture of  and 

A mixed solution of p-fluorophenol (0.32 g, 2.85 mmol) and sodium hydride (89 mg, 2.60 mmol) in anhydrous tetrahydrofuran (20 mL)-N,N-dimethylformamide (10 mL) was stirred under ice-cooling for 20 min. To the solution was added the mixture (0.82 g, 2.36 mmol) obtained in Reference Example 22 and the mixture was stirred at room temperature for 18 hrs. The reaction solution was diluted with ethyl acetate, washed successively with aqueous citric acid solution, water and aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated under reduced pressure. The obtained pale-yellow oil was dissolved in anhydrous tetrahydrofuran (30 mL) and the mixture was ice-cooled. To the solution was added dropwise 1.5 mol/l diisobutylaluminum hydride toluene solution (5.0 mL, 7.5 mmol). The solution was stirred under ice-cooling for 5 hrs. and dilute hydrochloric acid was added to the reaction solution. The mixture was extracted with ethyl acetate, washed with aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:10-1:5-1:3-1:1) to give a mixture (0.74 g) of the title compounds as a colorless oil. The mixture was used for the next reaction without separation (yield 93%).

MS m/z 319(M-OH)

Reference Example 24

methyl 3-[4-[(3-bromobenzyl)oxy]phenyl]propanoate

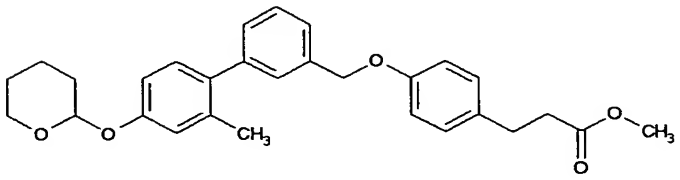


To a solution of methyl 3-(4-hydroxyphenyl)propanoate (0.3 g, 1.67 mmol) in N,N-dimethylformamide (4.0 mL) was added 60% sodium hydride (0.073 g, 1.83 mmol) at 0°C with stirring, and the mixture was stirred at the same temperature for 15 min. Then, 3-bromobenzylbromide (0.44 g, 1.75 mmol) was added to the mixture at 0°C with stirring, and the mixture was stirred at room temperature for 2 hrs. The reaction mixture was diluted with ethyl acetate and washed with 5% aqueous potassium hydrogensulfate solution and saturated brine. The ethyl acetate layer was dried over magnesium sulfate and concentrated under reduced pressure to give the title compound (0.84 g, yield 72%) as a colorless powder.

^{1}H NMR ($CDCl_3$) δ: 2.60(2H, t, J=7.8Hz), 2.90(2H, t, J=7.8Hz), 3.67(3H, s), 5.01(2H, s), 6.88(2H, d, J=8.4Hz), 7.12(2H, d, J=8.4Hz), 7.25(1H, m), 7.35(1H, d, J=7.5Hz), 7.45(1H, d, J=7.5Hz), 7.59(1H, s).

Example 1

methyl 3-(4-{[2'-methyl-4'-(tetrahydro-2H-pyran-2-yloxy)biphenyl-3-yl]methoxy}phenyl)propanoate



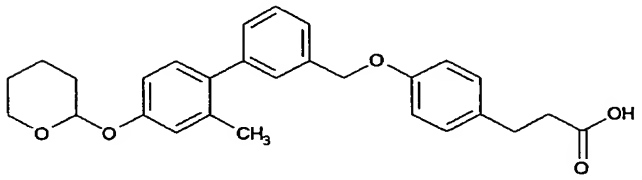
A solution of methyl 3-(4-hydroxyphenyl)propanoate (1.43 g, 7.94 mmol), [2'-methyl-4'-(tetrahydro-2H-pyran-2-yloxy)biphenyl-3-yl]methanol (2.37 g, 7.94 mmol) and tributylphosphine (2.97 mL, 11.9 mmol) in toluene (120 mL) was stirred under ice-cooling and 1,1'-(azodicarbonyl)dipiperidine (3.00 g, 11.9 mmol) was added by small portions. The mixture was warmed to room temperature and stirred for 24 hrs. Hexane (60 mL) was added to the reaction mixture and the precipitated insoluble material was filtered off. The filtrate was concentrated under reduced

pressure and the residue was purified by silica gel column chromatography (hexane-20% ethyl acetate/hexane) to give the title compound as a colorless oil (3.05 g, yield 83%).

^{1}H NMR ($CDCl_3$) δ: 1.58-1.75(3H, m), 1.85-1.90(2H, m), 1.97-2.08(1H, m), 2.23(3H, s), 2.60(2H, t, J=7.8Hz), 2.89(2H, t, J=7.8Hz), 3.61-3.66(4H, m), 3.91-3.99(1H, m), 5.07(2H, s), 5.46(1H, t, J=3.1Hz), 6.88-6.97(4H, m), 7.08-7.16(3H, m), 7.24-7.27(1H, m), 7.35-7.43(3H, m).

Example 2

3-(4-{[2'-methyl-4'-(tetrahydro-2H-pyran-2-yloxy)biphenyl-3-yl]methoxy}phenyl)propanoic acid

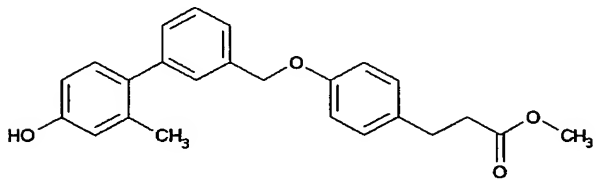


To a solution of methyl 3-(4-{[2'-methyl-4'-(tetrahydro-2H-pyran-2-yloxy)biphenyl-3-yl]methoxy}phenyl)propanoate (0.599 g, 1.30 mmol) in methanol (6 mL) and tetrahydrofuran (6 mL) was added 2 M aqueous sodium hydroxide solution (2 mL) and the mixture was stirred at room temperature for 24 hrs. Water was added to the reaction mixture, and the mixture was neutralized with 10% aqueous citric acid solution and extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-hexane to give the title compound (0.436 g, yield 75%) as colorless needle crystals.

^{1}H NMR ($CDCl_3$) δ: 1.58-1.76(3H, m), 1.85-1.90(2H, m), 1.97-2.10(1H, m), 2.23(3H, s), 2.65(2H, t, J=7.6Hz), 2.91(2H, t, J=7.6Hz), 3.60-3.66(1H, m), 3.91-3.99(1H, m), 5.08(2H, s), 5.46(1H, t, J=3.1Hz), 6.89-6.97(4H, m), 7.11-7.16(3H, m), 7.24-7.27(1H, m), 7.35-7.43(3H, m).

Example 3

methyl 3-{4-[(4'-hydroxy-2'-methylbiphenyl-3-yl)methoxy]phenyl}propanoate

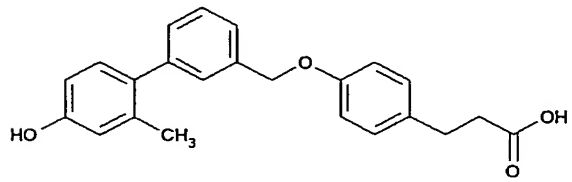


A solution of methyl 3-(4-{[2'-methyl-4'-(tetrahydro-2H-pyran-2-yloxy)biphenyl-3-yl]methoxy}phenyl)propanoate (3.78 g, 8.21 mmol) and p-toluenesulfonic acid monohydrate (0.156 g, 0.821 mmol) in methanol (60 mL) was stirred at room temperature for 2 hrs. The reaction solvent was evaporated under reduced pressure, and the residue was diluted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (20%-60% ethyl acetate/hexane) to give the title compound (3.04 g, yield 98%) as a colorless viscous oil.

MS m/z 377 (MH^+)

Example 4

3-{4-[(4'-hydroxy-2'-methylbiphenyl-3-yl)methoxy]phenyl}propanoic acid



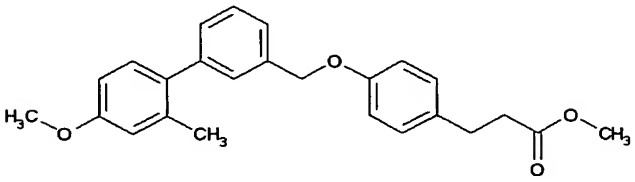
The title compound was obtained as colorless prism crystals from methyl 3-{4-[(4'-hydroxy-2'-methylbiphenyl-3-yl)methoxy]phenyl}propanoate according to a method similar to

the method of Example 2 (yield 31%, recrystallized from hexane-ethyl acetate).

^{1}H NMR ($CDCl_3$) δ: 2.21(3H, s), 2.65(2H, t, J=7.7Hz), 2.91(2H, t, J=7.7Hz), 5.07(2H, s), 6.69-6.75(2H, m), 6.92(2H, d, J=8.7Hz), 7.09-7.15(3H, m), 7.23-7.26(1H, m), 7.35-7.43(3H, m).

Example 5

methyl 3-{4-[(4'-methoxy-2'-methylbiphenyl-3-yl)methoxy]phenyl}propanoate

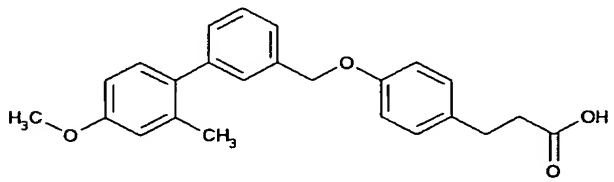


The title compound was obtained as a pale-yellow oil from methyl 3-{4-[(4'-hydroxy-2'-methylbiphenyl-3-yl)methoxy]phenyl}propanoate and methanol according to a method similar to the method of Example 1 (yield 92%).

^{1}H NMR ($CDCl_3$) δ: 2.24(3H, s), 2.60(2H, t, J=7.8Hz), 2.89(2H, t, J=7.8Hz), 3.66(3H, s), 3.83(3H, s), 5.07(2H, s), 6.77-6.82(2H, m), 6.91(2H, d, J=8.7Hz), 7.10-7.17(3H, m), 7.24-7.27(1H, m), 7.35-7.43(3H, m).

Example 6

3-{4-[(4'-methoxy-2'-methylbiphenyl-3-yl)methoxy]phenyl}propanoic acid



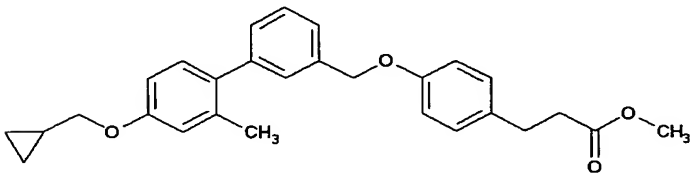
The title compound was obtained as colorless needle crystals from methyl 3-{4-[(4'-methoxy-2'-methylbiphenyl-3-yl)methoxy]phenyl}propanoate according to a method similar to

the method of Example 2 (yield 56%, recrystallized from hexane-ethyl acetate).

^{1}H NMR ($CDCl_3$) δ: 2.24(3H, s), 2.65(2H, t, J=7.7Hz), 2.91(2H, t, J=7.7Hz), 3.83(3H, s), 5.08(2H, s), 6.77-6.81(2H, m), 6.92(2H, d, J=8.7Hz), 7.11-7.18(3H, m), 7.24-7.27(1H, m), 7.36-7.44(3H, m).

Example 7

methyl 3-(4-{[4'-(cyclopropylmethoxy)-2'-methylbiphenyl-3-yl]methoxy}phenyl)propanoate

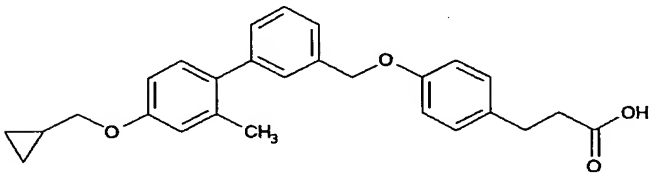


The title compound was obtained as a colorless oil from methyl 3-{4-[(4'-hydroxy-2'-methylbiphenyl-3-yl)methoxy]phenyl}propanoate and cyclopropylmethanol according to a method similar to the method of Example 1 (yield 85%).

MS m/z 431(MH^+)

Example 8

3-(4-{[4'-(cyclopropylmethoxy)-2'-methylbiphenyl-3-yl]methoxy}phenyl)propanoic acid

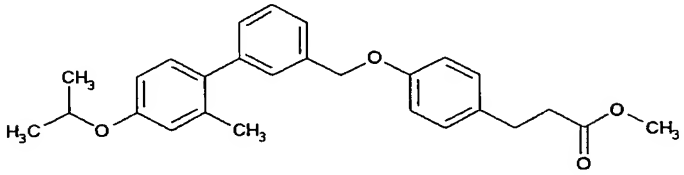


The title compound was obtained as colorless needle crystals from methyl 3-(4-{[4'-(cyclopropylmethoxy)-2'-methylbiphenyl-3-yl]methoxy}phenyl)propanoate according to a method similar to the method of Example 2 (yield 43%, recrystallized from hexane-ethyl acetate).

MS m/z 417(MH^+)

Example 9

methyl 3-{4-[(4'-isopropoxy-2'-methylbiphenyl-3-yl)methoxy]phenyl}propanoate

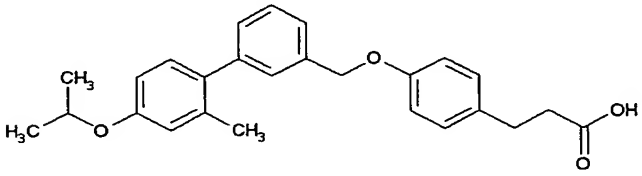


The title compound was obtained as a colorless oil from methyl 3-{4-[(4'-hydroxy-2'-methylbiphenyl-3-yl)methoxy]phenyl}propanoate and 2-propanol according to a method similar to the method of Example 1 (yield 78%).

MS m/z 419(MH^+)

Example 10

3-{4-[(4'-isopropoxy-2'-methylbiphenyl-3-yl)methoxy]phenyl}propanoic acid

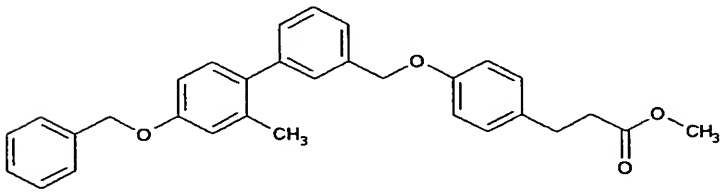


The title compound was obtained as colorless needle crystals from methyl 3-{4-[(4'-isopropoxy-2'-methylbiphenyl-3-yl)methoxy]phenyl}propanoate according to a method similar to the method of Example 2 (yield 56%, recrystallized from hexane-ethyl acetate).

MS m/z 405(MH^+)

Example 11

methyl 3-(4-{[4'-(benzyloxy)-2'-methylbiphenyl-3-yl]methoxy}phenyl)propanoate

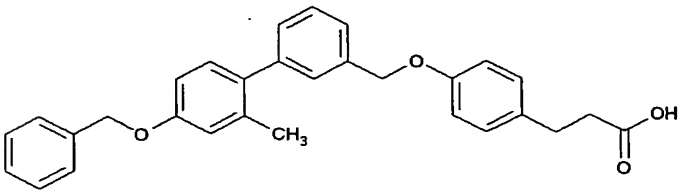


The title compound was obtained as a colorless oil from methyl 3-{4-[(4'-hydroxy-2'-methylbiphenyl-3-yl)methoxy]phenyl}propanoate and benzyl alcohol according to a method similar to the method of Example 1 (yield 79%).

MS m/z 467(MH^+)

Example 12

3-(4-{[4'-(benzyloxy)-2'-methylbiphenyl-3-yl]methoxy}phenyl)propanoic acid

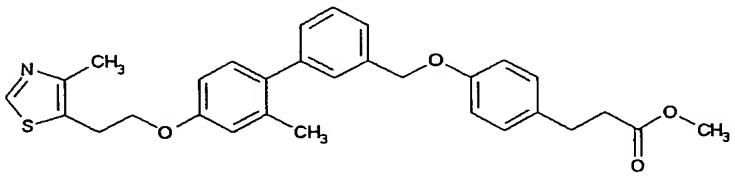


The title compound was obtained as colorless needle crystals from methyl 3-(4-{[4'-(benzyloxy)-2'-methylbiphenyl-3-yl]methoxy}phenyl)propanoate according to a method similar to the method of Example 2 (yield 45%, recrystallized from hexane-ethyl acetate).

MS m/z 453(MH^+)

Example 13

methyl 3-[4-({2'-methyl-4'-[2-(4-methyl-1,3-thiazol-5-yl)ethoxy]biphenyl-3-yl}methoxy)phenyl]propanoate

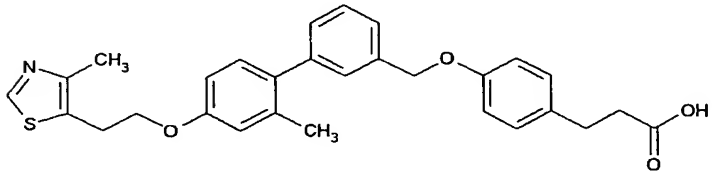


The title compound was obtained as a brown oil from methyl 3-{4-[(4'-hydroxy-2'-methylbiphenyl-3-yl)methoxy]phenyl}propanoate and 2-(4-methyl-1,3-thiazol-5-yl)ethanol according to a method similar to the method of Example 1 (yield 62%).

MS m/z 502(MH^+)

Example 14

3-[4-({2'-methyl-4'-[2-(4-methyl-1,3-thiazol-5-yl)ethoxy]biphenyl-3-yl}methoxy)phenyl]propanoic acid

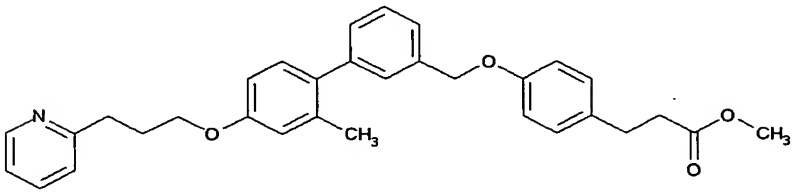


The title compound was obtained as colorless plate crystals from methyl 3-[4-({2'-methyl-4'-[2-(4-methyl-1,3-thiazol-5-yl)ethoxy]biphenyl-3-yl}methoxy)phenyl]propanoate according to a method similar to the method of Example 2 (yield 77%, recrystallized from hexane-ethyl acetate).

MS m/z 488(MH^+)

Example 15

methyl 3-(4-{[2'-methyl-4'-(3-(pyridin-2-yl)propoxy)biphenyl-3-yl]methoxy}phenyl)propanoate

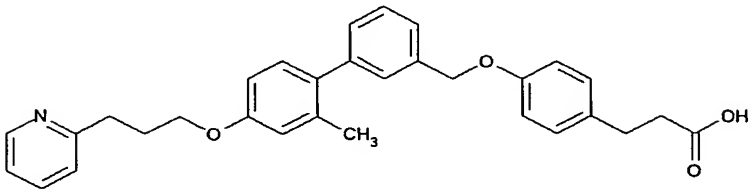


A solution of methyl 3-{4-[(4'-hydroxy-2'-methylbiphenyl-3-yl)methoxy]phenyl}propanoate (0.602 g, 1.60 mmol), 3-(pyridin-2-yl)propan-1-ol (0.822 g, 6.00 mmol) and triphenylphosphine (1.57 g, 6.00 mmol) in tetrahydrofuran (20 mL) under ice-cooling was stirred and diethyl azodicarboxylate (40% toluene solution, 2.72 mL, 6.00 mmol) was added. The mixture was warmed to room temperature and stirred for 42 hrs. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (20%-60% ethyl acetate/hexane) and preparative HPLC to give the title compound as a yellow viscous oil (0.446 g, yield 56%).

MS m/z 496(MH^+)

Example 16

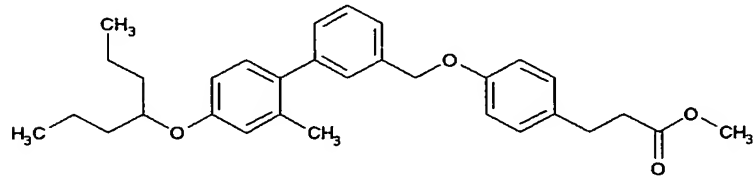
3-(4-{[2'-methyl-4'-(3-(pyridin-2-yl)propoxy)biphenyl-3-yl]methoxy}phenyl)propanoic acid



A solution of methyl 3-(4-{[2'-methyl-4'-(3-(pyridin-2-yl)propoxy)biphenyl-3-yl]methoxy}phenyl)propanoate (0.401 g, 0.809 mmol) in methanol (5 mL) and tetrahydrofuran (5 mL) was added 2 M aqueous sodium hydroxide solution (1.5 mL) and the mixture was stirred at room temperature for 75 hrs. Water was added to the reaction mixture, and the mixture was neutralized with 10% aqueous citric acid solution and extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (50% ethyl acetate/hexane-ethyl acetate) and recrystallized from ethyl acetate-hexane to give the title compound (0.186 g, yield 48%) as colorless prism crystals.
MS m/z 482(MH^+)

Example 17

methyl 3-(4-{[2'-methyl-4'-(1-propylbutoxy)biphenyl-3-yl]methoxy}phenyl)propanoate

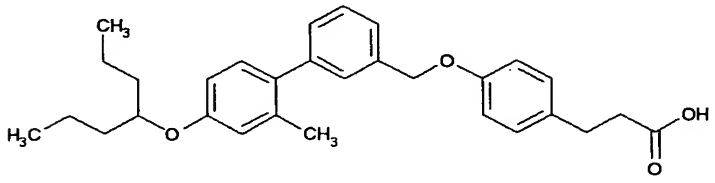


The title compound was obtained as a colorless oil from methyl 3-{4-[(4'-hydroxy-2'-methylbiphenyl-3-yl)methoxy]phenyl}propanoate and 4-heptanol according to a method similar to the method of Example 1 (yield 65%).

^{1}H NMR ($CDCl_3$) δ: 0.94(6H, t, J=7.2Hz), 1.31-1.81(8H, m), 2.22(3H, s), 2.60(2H, t, J=7.8Hz), 2.89(2H, t, J=7.8Hz), 3.66(3H, s) 4.23-4.31(1H, m), 5.07(2H, s), 6.74-6.80(2H, m), 6.88-6.93(2H, m), 7.10-7.16(3H, m), 7.25-7.28(1H, m), 7.36-7.43(3H, m).

Example 18

3-(4-{[2'-methyl-4'-(1-propylbutoxy)biphenyl-3-yl]methoxy}phenyl)propanoic acid

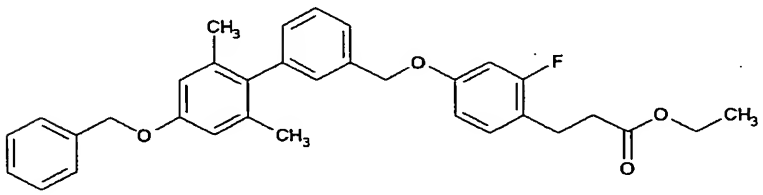


The title compound was obtained as colorless needle crystals from methyl 3-(4-{[2'-methyl-4'-(1-propylbutoxy)biphenyl-3-yl]methoxy}phenyl)propanoate according to a method similar to the method of Example 2 (yield 77%, recrystallized from hexane-ethyl acetate).

^{1}H NMR ($CDCl_3$) δ: 0.94(6H, t, J=7.3Hz), 1.33-1.76(8H, m), 2.22(3H, s), 2.65(2H, t, J=7.7Hz), 2.91(2H, t, J=7.7Hz), 4.23-4.31(1H, m), 5.07(2H, s), 6.73-6.80(2H, m), 6.92(2H, d, J=8.6Hz), 7.13(3H, d, J=8.6Hz), 7.24-7.28(1H, m), 7.35-7.43(3H, m).

Example 19

ethyl 3-(4-{[4'-(benzyloxy)-2',6'-dimethylbiphenyl-3-yl]methoxy}-2-fluorophenyl)propanoate

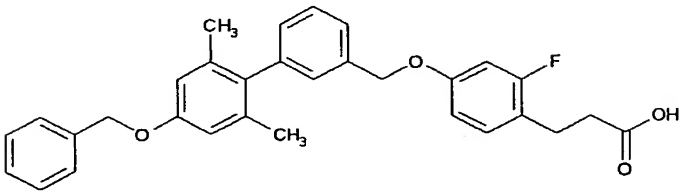


The title compound was obtained as a colorless oil from ethyl 3-(2-fluoro-4-hydroxyphenyl)propanoate and [4'-(benzyloxy)-2',6'-dimethylbiphenyl-3-yl]methanol according to a method similar to the method of Example 1 (yield 76%).

MS m/z 513(MH^+)

Example 20

3-(4-{[4'-(benzyloxy)-2',6'-dimethylbiphenyl-3-yl]methoxy}-2-fluorophenyl)propanoic acid

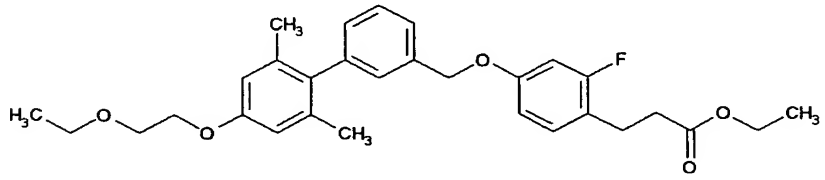


The title compound was obtained as colorless prism crystals from ethyl 3-(4-{[4'-(benzyloxy)-2',6'-dimethylbiphenyl-3-yl]methoxy}-2-fluorophenyl)propanoate according to a method similar to the method of Example 2 (yield 57%, recrystallized from heptane-ethyl acetate).

MS m/z 485(MH^+)

Example 21

ethyl 3-(4-{[4'-(2-ethoxyethoxy)-2',6'-dimethylbiphenyl-3-yl]methoxy}-2-fluorophenyl)propanoate

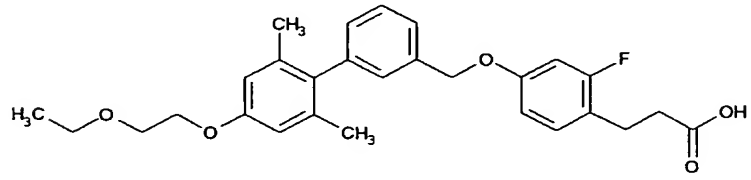


The title compound was obtained as a colorless oil from ethyl 3-(2-fluoro-4-hydroxyphenyl)propanoate and [4'-(2-ethoxyethoxy)-2',6'-dimethylbiphenyl-3-yl]methanol according to a method similar to the method of Example 1 (yield 93%).

MS m/z 495(MH^+)

Example 22

3-(4-{[4'-(2-ethoxyethoxy)-2',6'-dimethylbiphenyl-3-yl]methoxy}-2-fluorophenyl)propanoic acid

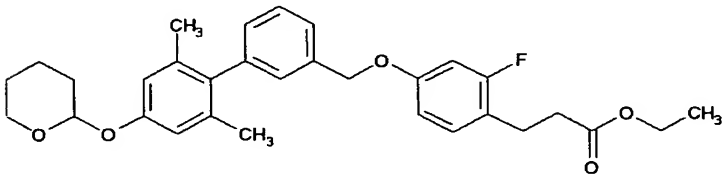


The title compound was obtained as colorless prism crystals from ethyl 3-(4-{[4'-(2-ethoxyethoxy)-2',6'-dimethylbiphenyl-3-yl]methoxy}-2-fluorophenyl)propanoate according to a method similar to the method of Example 2 (yield 77%, recrystallized from hexane-ethyl acetate).

MS m/z 467(MH^+)

Example 23

ethyl 3-(4-{[2',6'-dimethyl-4'-(tetrahydro-2H-pyran-2-yloxy)biphenyl-3-yl]methoxy}-2-fluorophenyl)propanoate

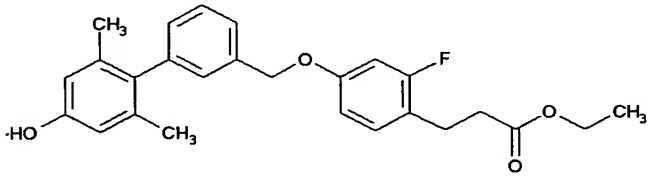


The title compound was obtained as a colorless oil from ethyl 3-(2-fluoro-4-hydroxyphenyl)propanoate and [2',6'-dimethyl-4'-(tetrahydro-2H-pyran-2-yloxy)biphenyl-3-yl]methanol according to a method similar to the method of Example 1 (yield 89%).

MS m/z 507(MH^+)

Example 24

ethyl 3-{2-fluoro-4-[(4'-hydroxy-2',6'-dimethylbiphenyl-3-yl)methoxy]phenyl}propanoate

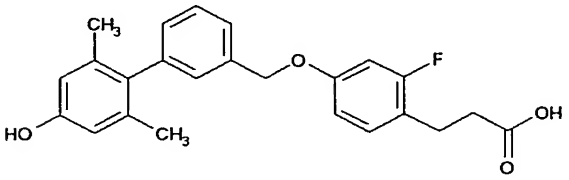


The title compound was obtained as a colorless oil from ethyl 3-(4-{[2',6'-dimethyl-4'-(tetrahydro-2H-pyran-2-yloxy)biphenyl-3-yl]methoxy}-2-fluorophenyl)propanoate according to a method similar to the method of Example 3 (yield 97%).

MS m/z 423(MH^+)

Example 25

3-{2-fluoro-4-[(4'-hydroxy-2',6'-dimethylbiphenyl-3-yl)methoxy]phenyl}propanoic acid

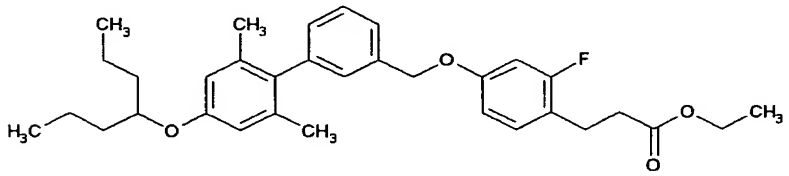


The title compound was obtained as colorless prism crystals from ethyl 3-{2-fluoro-4-[(4'-hydroxy-2',6'-dimethylbiphenyl-3-yl)methoxy]phenyl}propanoate according to a method similar to the method of Example 2 (yield 82%, recrystallized from hexane-ethyl acetate).

MS m/z 395(MH^+)

Example 26

ethyl 3-(4-{[2',6'-dimethyl-4'-(1-propylbutoxy)biphenyl-3-yl]methoxy}-2-fluorophenyl)propanoate

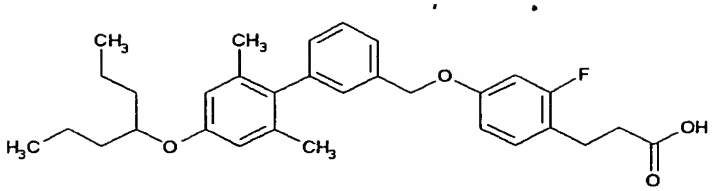


The title compound was obtained as a colorless oil from ethyl 3-{2-fluoro-4-[(4'-hydroxy-2',6'-dimethylbiphenyl-3-yl)methoxy]phenyl}propanoate and 4-heptanol according to a method similar to the method of Example 1 (yield 88%).

^1H NMR ($CDCl_3$) δ: 0.94(6H, t, J=7.2Hz), 1.23(3H, t, J=7.2Hz), 1.33-1.76(8H, m), 1.98(6H, s), 2.57(2H, t, J=7.6Hz), 2.89(2H, t, J=7.6Hz), 4.12(2H, q, J=7.2Hz), 4.21-4.29(1H, m), 5.06(2H, s), 6.62-6.70(4H, m), 7.05-7.12(2H, m), 7.18(1H, s), 7.33-7.38(1H, m), 7.42(1H, t, J=7.5Hz).

Example 27

3-(4-{[2',6'-dimethyl-4'-(1-propylbutoxy)biphenyl-3-yl]methoxy}-2-fluorophenyl)propanoic acid

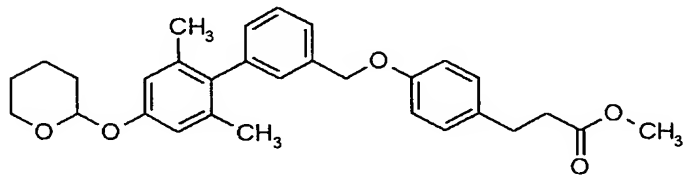


The title compound was obtained as colorless needle crystals from ethyl 3-(4-{[2',6'-dimethyl-4'-(1-propylbutoxy)biphenyl-3-yl]methoxy}-2-fluorophenyl)propanoate according to a method similar to the method of Example 2 (yield 62%, recrystallized from heptane-ethyl acetate).

^{1}H NMR ($CDCl_3$) δ: 0.94(6H, t, J=7.3Hz), 1.33-1.76(8H, m), 1.97(6H, s), 2.64(2H, t, J=7.6Hz), 2.91(2H, t, J=7.6Hz), 4.21-4.29(1H, m), 5.06(2H, s), 6.63-6.71(4H, m), 7.06-7.13(2H, m), 7.18(1H, s), 7.33-7.38(1H, m), 7.42(1H, t, J=7.4Hz).

Example 28

methyl 3-[4-[[2',6'-dimethyl-4'-(tetrahydro-2H-pyran-2-yloxy)biphenyl-3-yl]methoxy]phenyl]propanoate

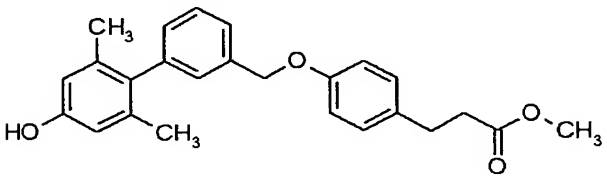


To a solution of methyl 3-(4-hydroxyphenyl)propanoate (3.28 g, 18.2 mmol), [2',6'-dimethyl-4'-(tetrahydro-2H-pyran-2-yloxy)biphenyl-3-yl]methanol (5.15 g, 16.5 mmol) and triphenylphosphine (5.63 g, 21.5 mmol) in tetrahydrofuran (100 mL) was added dropwise diethyl azodicarboxylate (40% toluene solution, 9.7 mL) at 0°C with stirring, and the mixture was stirred at room temperature for 48 hrs. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (hexane/ethyl acetate=10/1-hexane/ethyl acetate=3/1) to give the title compound (2.92 g, yield 37%) as a yellow oil.

^{1}H NMR ($CDCl_3$) δ: 1.57-1.78(3H, m), 1.82-1.90(2H, m), 1.98(6H, s), 2.02(1H, m), 2.59(2H, t, J=7.8Hz), 2.89(2H, t, J=7.8Hz), 3.62(1H, m), 3.66(3H, s), 3.97(1H, m), 5.08(2H, s), 5.45(1H, t, J=3.0Hz), 6.81(2H, s), 6.89(2H, d, J=8.4Hz), 7.05-7.14(3H, m), 7.18(1H, s), 7.34-7.47(2H, m).

Example 29

methyl 3-[4-[(4'-hydroxy-2',6'-dimethylbiphenyl-3-yl)methoxy]phenyl]propanoate

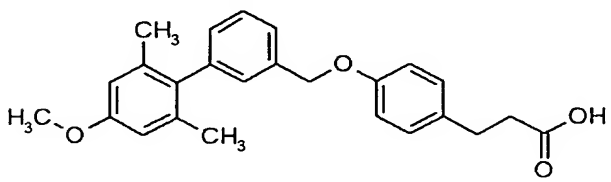


A mixture of methyl 3-[4-[[2',6'-dimethyl-4'-(tetrahydro-2H-pyran-2-yloxy)biphenyl-3-yl]methoxy]phenyl]propanoate (2.92 g, 6.15 mmol), p-toluenesulfonic acid monohydrate (0.12 g, 0.62 mmol) and methanol (60 mL) was stirred at room temperature for 2 hrs., and the mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=10/1-hexane/ethyl acetate=1/2) to give the title compound (2.12 g, yield 88%) as a red oil.

^{1}H NMR ($CDCl_3$) δ: 1.96(6H, s), 2.59(2H, t, J=7.8Hz), 2.89(2H, t, J=7.8Hz), 3.66(3H, s), 4.63(1H, s), 5.08(2H, s), 6.59(2H, s), 6.89(2H, d, J=8.7Hz), 7.05-7.13(3H, m), 7.17(1H, s), 7.35-7.45(2H, m).

Example 30

3-[4-[(4'-methoxy-2',6'-dimethylbiphenyl-3-yl)methoxy]phenyl]propanoic acid



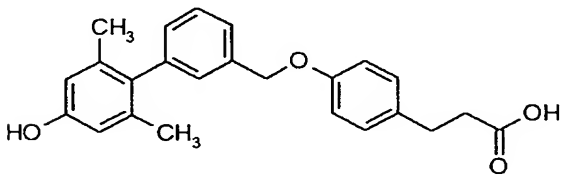
To a solution of methyl 3-[4-[(4'-hydroxy-2',6'-dimethylbiphenyl-3-yl)methoxy]phenyl]propanoate (0.20 g, 0.51 mmol), methanol (0.041 mL, 1.02 mmol) and triphenylphosphine (0.18 g, 0.67 mmol) in tetrahydrofuran (4.0 mL) was added dropwise diethyl azodicarboxylate (40% toluene solution, 0.30 mL) at 0°C with stirring and the mixture was stirred at room temperature for 12 hrs. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (hexane/ethyl acetate=10/1-hexane/ethyl acetate=3/1) to give a yellow oil (0.13 g, yield 65%).

To a mixture of the product obtained, methanol (2 mL) and tetrahydrofuran (4 mL) was added 1 N aqueous sodium hydroxide solution (0.66 mL) at room temperature with stirring and the mixture was stirred at the same temperature for 1 hr. The reaction mixture was adjusted to pH3 with 1 N hydrochloric acid, and the mixture was partitioned and extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=4/1-hexane/ethyl acetate=1/2) to give the title compound (0.12 g, yield 89%) as colorless crystals.

MS(APCI-): 389(M-H)

Example 31

3-[4-[(4'-hydroxy-2',6'-dimethylbiphenyl-3-yl)methoxy]phenyl]propanoic acid



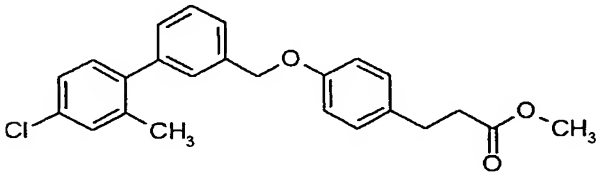
To a solution of methyl 3-[4-[(4'-hydroxy-2',6'-dimethylbiphenyl-3-yl)methoxy]phenyl]propanoate (0.18 g, 0.46

mmol) in methanol (2 mL) and tetrahydrofuran (4 mL) was added 1 N aqueous sodium hydroxide solution (0.91 mL) and the mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated and the residue was diluted with ethyl acetate, washed with 1 N hydrochloric acid and saturated brine, dried and concentrated under reduced pressure. The residue was crystallized from hexane/ethyl acetate=4/1 to give the title compound (0.13 g, yield 74%) as colorless crystals.

MS(APCI-): 375(M-H)

Example 32

methyl 3-[4-[(4'-chloro-2'-methylbiphenyl-3-yl)methoxy]phenyl]propanoate

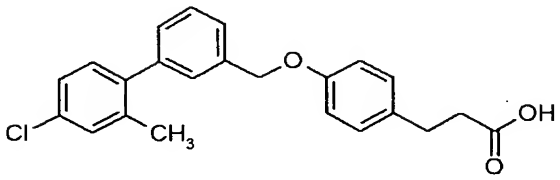


A mixture of methyl 3-[4-[(3-bromobenzyl)oxy]phenyl]propanoate (0.5 g, 1.43 mmol), 4-chloro-2-methylphenylboronic acid (0.30 g, 1.72 mmol), tetrakis(triphenylphosphine)palladium(0) (0.083 g, 0.072 mmol), sodium carbonate (0.46 g, 4.29 mmol), water (5 mL), ethanol (5 mL) and toluene (25 mL) was stirred under an argon atmosphere at 90°C for 16 hrs. The reaction mixture was cooled, diluted with ethyl acetate, washed with water and saturated brine, dried and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=10/1-4/1) to give the title compound (0.50 g, yield 88%) as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 2.22(3H, s), 2.60(2H, t, J=7.8Hz), 2.90(2H, t, J=7.8Hz), 3.66(3H, s), 5.08(2H, s), 6.91(2H, d, J=8.7Hz), 7.08-7.28(6H, m), 7.34(1H, br), 7.38-7.46(2H, m).

Example 33

3-[4-[(4'-chloro-2'-methylbiphenyl-3-yl)methoxy]phenyl]propanoic acid

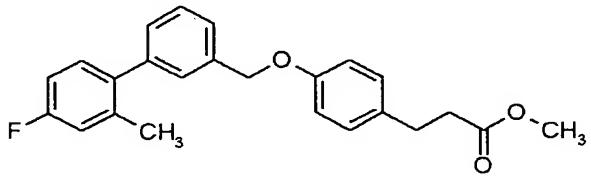


The title compound was obtained as colorless crystals from methyl 3-[4-[(4'-chloro-2'-methylbiphenyl-3-yl)methoxy]phenyl]propanoate according to a method similar to the method of Example 31 (yield 73%).

MS(APCI-): 379(M-H), 381

Example 34

methyl 3-[4-[(4'-fluoro-2'-methylbiphenyl-3-yl)methoxy]phenyl]propanoate

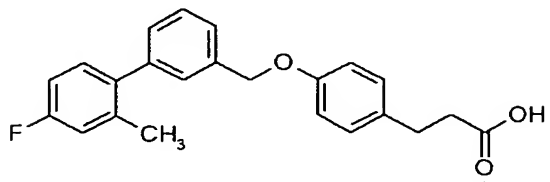


The title compound was obtained as colorless crystals from methyl 3-[4-[(3-bromobenzyl)oxy]phenyl]propanoate and 4-fluoro-2-methylphenylboronic acid according to a method similar to the method of Example 32 (yield 94%).

^{1}H NMR ($CDCl_3$) δ: 2.23(3H, s), 2.60(2H, t, J=7.8Hz), 2.90(2H, t, J=7.8Hz), 3.66(3H, s), 5.08(2H, s), 6.86-7.00(4H, m), 7.07-7.28(4H, m), 7.31-7.46(3H, m).

Example 35

3-[4-[(4'-fluoro-2'-methylbiphenyl-3-yl)methoxy]phenyl]propanoic acid

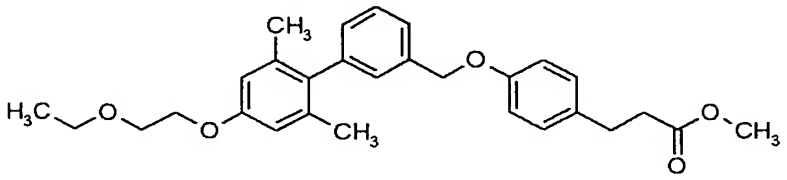


The title compound was obtained as colorless crystals from methyl 3-[4-[(4'-fluoro-2'-methylbiphenyl-3-yl)methoxy]phenyl]propanoate according to a method similar to the method of Example 31 (yield 81%).

MS(APCI-): 363(M-H)

Example 36

methyl 3-[4-[[4'-(2-ethoxyethoxy)-2',6'-dimethylbiphenyl-3-yl]methoxy]phenyl]propanoate

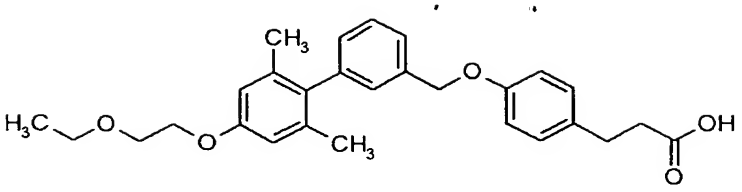


To a solution of methyl 3-[4-[(4'-hydroxy-2',6'-dimethylbiphenyl-3-yl)methoxy]phenyl]propanoate (0.20 g, 0.51 mmol), 2-ethoxyethanol (0.099 mL, 1.02 mmol) and triphenylphosphine (0.18 g, 0.67 mmol) in tetrahydrofuran (4.0 mL) was added dropwise diethyl azodicarboxylate (40% toluene solution, 0.30 mL) at 0°C with stirring and the mixture was stirred at room temperature for 12 hrs. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (hexane/ethyl acetate=10/1-hexane/ethyl acetate=3/1) to give the title compound (0.12 g, yield 51%) as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 1.25(3H, t, J=6.9Hz), 1.98(6H, s), 2.59(2H, t, J=7.8Hz), 2.89(2H, t, J=7.8Hz), 3.62(2H, q, J=6.9Hz), 3.66(3H, s), 3.80(2H, t, J=5.1Hz), 4.14(2H, t, J=5.1Hz), 5.08(2H, s), 6.68(2H, s), 6.89(2H, d, J=8.4Hz), 7.04-7.14(3H, m), 7.17(1H, s), 7.35-7.45(2H, m).

Example 37

3-[4-[[4'-(2-ethoxyethoxy)-2',6'-dimethylbiphenyl-3-yl]methoxy]phenyl]propanoic acid

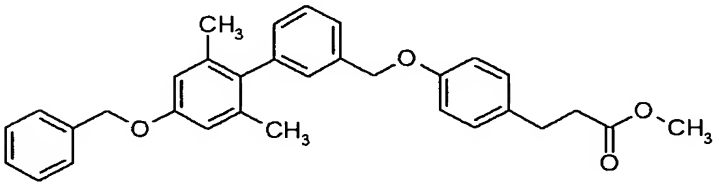


Methyl 3-[4-[[4'-(2-ethoxyethoxy)-2',6'-dimethylbiphenyl-3-yl]methoxy]phenyl]propanoate (0.12 g, 0.26 mmol) was dissolved in a mixed solution of methanol (2 mL) and tetrahydrofuran (4 mL), and 1 N aqueous sodium hydroxide solution (0.52 mL) was added at room temperature with stirring. The mixture was stirred at the same temperature for 2 hrs. After the completion of the reaction, the reaction mixture was diluted with ethyl acetate, washed successively with 1 N hydrochloric acid, water and saturated brine, dried and concentrated under reduced pressure. The residue was crystallized from hexane/ethyl acetate=4/1 to give the title compound (0.087 g, yield 75%) as colorless crystals.

MS(APCI-): 447(M-H)

Example 38

methyl 3-[4-[[4'-(benzyloxy)-2',6'-dimethylbiphenyl-3-yl]methoxy]phenyl]propanoate

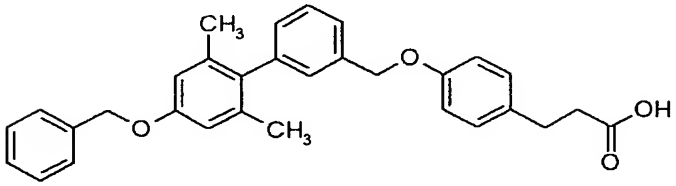


The title compound was obtained as a colorless oil from methyl 3-[4-[(4'-hydroxy-2',6'-dimethylbiphenyl-3-yl)methoxy]phenyl]propanoate and benzyl alcohol according to a method similar to the method of Example 36 (yield 63%).

^{1}H NMR ($CDCl_3$) δ: 1.99(6H, s), 2.59(2H, t, J=7.8Hz), 2.89(2H, t, J=7.8Hz), 3.66(3H, s), 5.07(2H, s), 5.08(2H, s), 6.75(2H, s), 6.89(2H, d, J=8.7Hz), 7.05-7.13(3H, m), 7.18(1H, s), 7.30-7.49(7H, m).

Example 39

3-[4-[[4'-(benzyloxy)-2',6'-dimethylbiphenyl-3-yl]methoxy]phenyl]propanoic acid

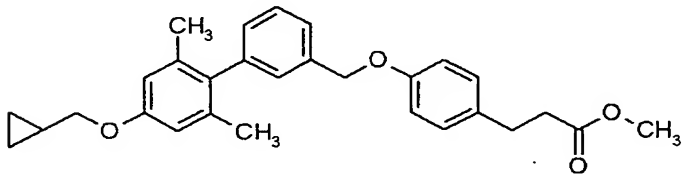


The title compound was obtained as colorless crystals from methyl 3-[4-[[4'-(benzyloxy)-2',6'-dimethylbiphenyl-3-yl]methoxy]phenyl]propanoate according to a method similar to the method of Example 37 (yield 91%).

MS(APCI-): 465(M-H).

Example 40

methyl 3-[4-[[4'-(cyclopropylmethoxy)-2',6'-dimethylbiphenyl-3-yl]methoxy]phenyl]propanoate

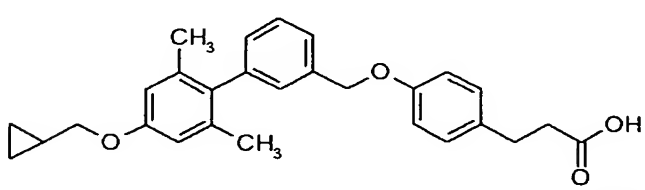


The title compound was obtained as a colorless oil from methyl 3-[4-[(4'-hydroxy-2',6'-dimethylbiphenyl-3-yl)methoxy]phenyl]propanoate and cyclopropylmethanol according to a method similar to the method of Example 36 (yield 69%).

^{1}H NMR ($CDCl_3$) δ: 0.31-0.39(2H, m), 0.60-0.69(2H, m), 1.27(1H, m), 1.98(6H, s), 2.59(2H, t, J=7.8Hz), 2.89(2H, t, J=7.8Hz), 3.66(3H, s), 3.81(2H, d, J=6.9Hz), 5.08(2H, s), 6.66(2H, s), 6.89(2H, d, J=8.7Hz), 7.05-7.13(3H, m), 7.18(1H, s), 7.35-7.45(2H, m).

Example 41

3-[4-[[4'-(cyclopropylmethoxy)-2',6'-dimethylbiphenyl-3-yl]methoxy]phenyl]propanoic acid

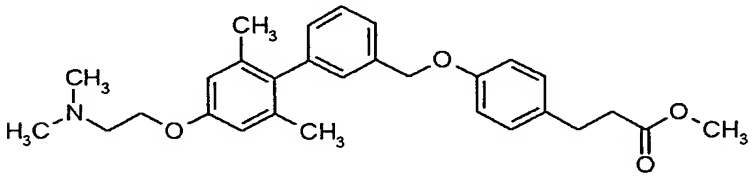


The title compound was obtained as colorless crystals from methyl 3-[4-[[4'-(cyclopropylmethoxy)-2',6'-dimethylbiphenyl-3-yl]methoxy]phenyl]propanoate according to a method similar to the method of Example 37 (yield 76%).

MS(APCI-): 429(M-H)

Example 42

methyl 3-[4-[[4'-[2-(dimethylamino)ethoxy]-2',6'-dimethylbiphenyl-3-yl]methoxy]phenyl]propanoate

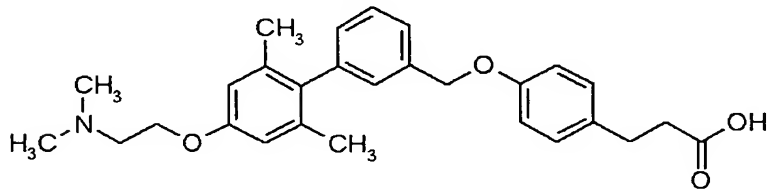


The title compound was obtaiend as a colorless oil from methyl 3-[4-[(4'-hydroxy-2',6'-dimethylbiphenyl-3-yl)methoxy]phenyl]propanoate and N,N-dimethylethanolamine according to a method similar to the method of Example 36 (yield 38%).

^{1}H NMR ($CDCl_3$) δ: 1.98(6H, s), 2.35(6H, s), 2.59(2H, t, J=7.8Hz), 2.75(2H, t, J=5.7Hz), 2.89(2H, t, J=7.8Hz), 3.66(3H, s), 4.09(2H, t, J=5.7Hz), 5.08(2H, s), 6.68(2H, s), 6.89(2H, d, J=8.7Hz), 7.05-7.13(3H, m), 7.18(1H, s), 7.35-7.45(2H, m).

Example 43

3-[4-[[4'-[2-(dimethylamino)ethoxy]-2',6'-dimethylbiphenyl-3-yl]methoxy]phenyl]propanoic acid trifluoroacetate



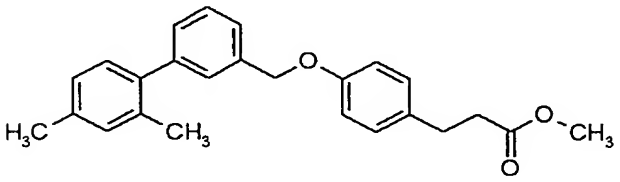
The title compound was obtained from methyl 3-[4-[[4'-[2-(dimethylamino)ethoxy]-2',6'-dimethylbiphenyl-3-yl]methoxy]phenyl]propanoate according to a method similar to

the method of Example 37. This compound was purified by preparative HPLC. Colorless crystals (yield 87%)

MS(APCI-): 446(M-H, as a free form)

Example 44

methyl 3-{4-[(2',4'-dimethylbiphenyl-3-yl)methoxy]phenyl}propanoate

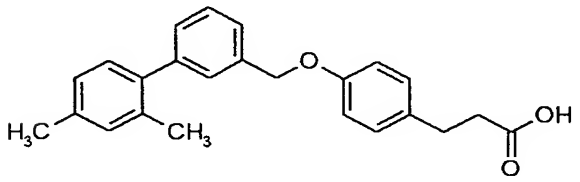


The title compound was synthesized from methyl 3-(4-hydroxyphenyl)propanoate and (2',4'-dimethylbiphenyl-3-yl)methanol according to a method similar to the method of Example 1 (yield 83%).

MS m/z 375 (MH^+)

Example 45

3-{4-[(2',4'-dimethylbiphenyl-3-yl)methoxy]phenyl}propanoic acid

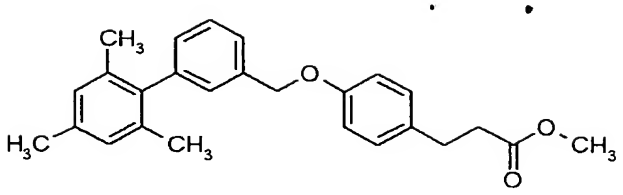


The title compound was synthesized from methyl 3-{4-[(2',4'-dimethylbiphenyl-3-yl)methoxy]phenyl}propanoate according to a method similar to the method of Example 2 (yield 91%).

^1H NMR ($CDCl_3$) δ: 2.22(3H,s), 2.36(3H,s), 2.65(2H,t,J=7.6Hz), 2.91(2H,t,J=7.6Hz), 5.08(2H,s), 6.91(2H,d,J=8.4Hz), 7.00-7.46(9H,m).

Example 46

methyl 3-{4-[(2',4',6'-trimethylbiphenyl-3-yl)methoxy]phenyl}propanoate

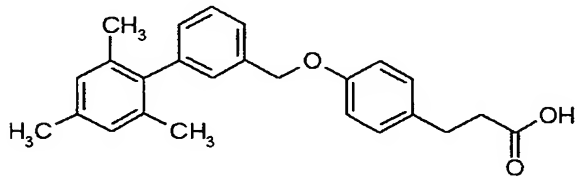


The title compound was synthesized from methyl 3-(4-hydroxyphenyl)propanoate and (2',4',6'-trimethylbiphenyl-3-yl)methanol according to a method similar to the method of Example 1 (yield 71%).

^{1}H NMR ($CDCl_3$) δ: 1.98(6H,s), 2.32(3H,s), 2.59(2H,t,J=7.6Hz), 2.89(2H,t,J=7.6Hz), 3.66(3H,s), 5.08(2H,s), 6.88(2H,d,J=8.8Hz), 6.93(2H,s), 7.05-7.48(6H,m).

Example 47

3-{4-[(2',4',6'-trimethylbiphenyl-3-yl)methoxy]phenyl}propanoic acid

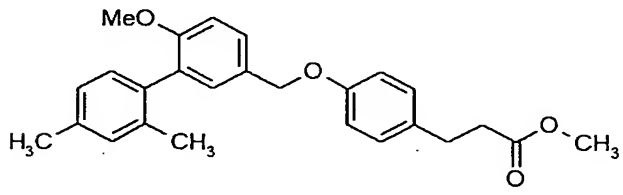


The title compound was synthesized from methyl 3-{4-[(2',4',6'-trimethylbiphenyl-3-yl)methoxy]phenyl}propanoate according to a method similar to the method of Example 2 (yield 88%).

^{1}H NMR ($CDCl_3$) δ: 1.98(6H,s), 2.32(3H,s), 2.64(2H,t,J=7.4Hz), 2.90(2H,t,J=7.4Hz), 5.08(2H,s), 6.89(2H,d,J=8.8Hz), 6.93(2H,s), 7.04-7.48(6H,m).

Example 48

methyl 3-(4-((6-methoxy-2',4'-dimethylbiphenyl-3-yl)methoxy)phenyl)propanoate

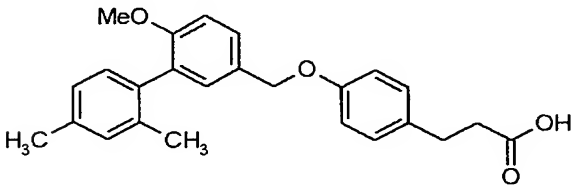


The title compound was synthesized from methyl 3-(4-hydroxyphenyl)propanoate and (6-methoxy-2',4'-dimethylbiphenyl-3-yl)methanol according to a method similar to the method of Example 1 (yield 68%).

^{1}H NMR ($CDCl_3$) δ: 2.10(3H,s), 2.36(3H,s), 2.59(2H,t,J=7.6Hz), 2.90(2H,t,J=7.6Hz), 3.66(3H,s), 3.77(3H,s), 4.98(2H,s), 6.90(2H,d,J=8.8Hz), 6.95(1H,d,J=8.4Hz), 7.00-7.17(5H,m), 7.20(1H,d,J=2.2Hz), 7.39(1H,dd,J=2.2 & 8.4Hz).

Example 49

3-(4-((6-methoxy-2',4'-dimethylbiphenyl-3-yl)methoxy)phenyl)propanoic acid

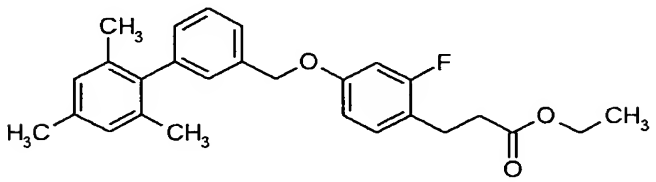


The title compound was synthesized from methyl 3-(4-((6-methoxy-2',4'-dimethylbiphenyl-3-yl)methoxy)phenyl)propanoate according to a method similar to the method of Example 2 (yield 100%).

^{1}H NMR ($CDCl_3$) δ: 2.10(3H,s), 2.36(3H,s), 2.65(2H,t,J=7.6Hz), 2.91(2H,t,J=7.6Hz), 3.77(3H,s), 4.99(2H,s), 6.84-7.18(8H,m), 7.20(1H,d,J=2.2Hz), 7.39(1H,dd,J=2.6 & 8.4Hz).

Example 50

ethyl 3-{2-fluoro-4-[(2',4',6'-trimethylbiphenyl-3-yl)methoxy]phenyl}propanoate



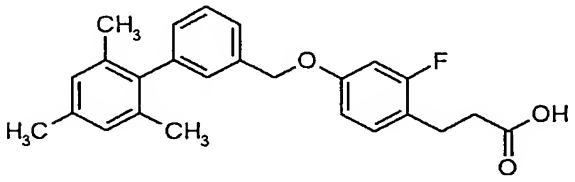
The title compound was synthesized from ethyl 3-(2-fluoro-4-hydroxyphenyl)propanoate and (2',4',6'-trimethylbiphenyl-3-

yl)methanol according to a method similar to the method of Example 1 (yield 74%).

MS m/z 421 (MH^+)

Example 51

3-{2-fluoro-4-[(2',4',6'-trimethylbiphenyl-3-yl)methoxy]phenyl}propanoic acid

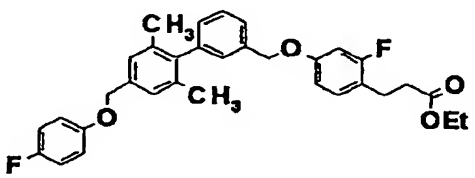
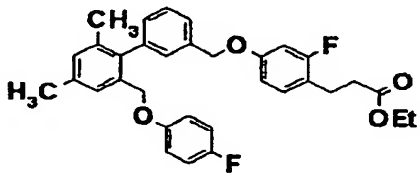


The title compound was synthesized from ethyl 3-{2-fluoro-4-[(2',4',6'-trimethylbiphenyl-3-yl)methoxy]phenyl}propanoate according to a method similar to the method of Example 2 (yield 77%).

APCI(-) 391 (M-H)

Example 52 and 53

ethyl 3-{2-fluoro-4-[(2'-(4-fluorophenoxymethyl)-4',6'-dimethylbiphenyl-3-yl)methoxy]phenyl}propanoate (Example 52) and ethyl 3-{2-fluoro-4-[(4'-(4-fluorophenoxymethyl)-2',6'-dimethylbiphenyl-3-yl)methoxy]phenyl}propanoate (Example 53)

Mixture of  and 

To a solution of the mixture (0.74 g, 2.20 mmol) obtained in Reference Example 23, ethyl 3-(2-fluoro-4-hydroxyphenyl)propanoate (0.47 g, 2.21 mmol) and tributylphosphine (0.71 mL, 2.85 mmol) in anhydrous tetrahydrofuran (40 mL) was added 1,1'-(azodicarbonyl)dipiperidine (0.72 g, 2.85 mmol) by small portions, and the mixture was stirred at room temperature for 18 hrs. The reaction mixture was diluted with diethyl ether (40 mL) and the precipitate was filtered off and the filtrate was

concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=1:10-1:5) to give a mixture (1.08 g) of the title compounds as a pale-yellow oil. The mixture was used for the next reaction without separation (yield 93%).

MS m/z 531(MH^+)

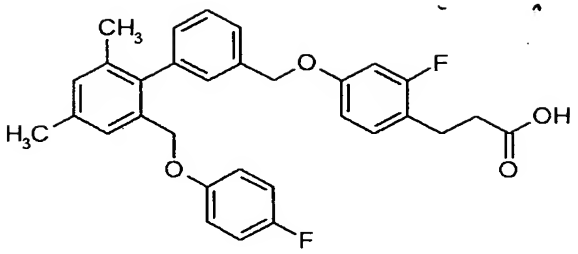
Example 54 and 55

3-{2-fluoro-4-[(2'-(4-fluorophenoxymethyl)-4',6'-dimethylbiphenyl-3-yl)methoxy]phenyl}propanoic acid (Example 54) and 3-{2-fluoro-4-[(4'-(4-fluorophenoxymethyl)-2',6'-dimethylbiphenyl-3-yl)methoxy]phenyl}propanoic acid (Example 55)

A mixture (1.08 g, 2.04 mmol) of ethyl 3-{2-fluoro-4-[(2'-(4-fluorophenoxymethyl)-4',6'-dimethylbiphenyl-3-yl)methoxy]phenyl}propanoate and ethyl 3-{2-fluoro-4-[(4'-(4-fluorophenoxymethyl)-2',6'-dimethylbiphenyl-3-yl)methoxy]phenyl}propanoate obtained in Examples 52 and 53 was dissolved in a mixed solvent of tetrahydrofuran (10 mL) and ethanol (10 mL). To the solution was added an aqueous solution (5 mL) of 85% potassium hydroxide (0.34 g, 5.15 mmol) and the mixture was stirred at room temperature for 18 hrs. The reaction solution was diluted with ethyl acetate, washed successively with aqueous citric acid solution, water and aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated under reduced pressure. The obtained residue was applied to chiral column (CHIRALPAK) chromatography (hexane:2-propanol:acetic acid=94:6:0.1) to purify each steric isomer.

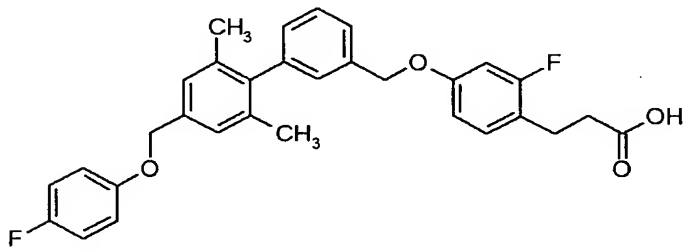
3-{2-Fluoro-4-[(2'-(4-fluorophenoxymethyl)-4',6'-dimethylbiphenyl-3-yl)methoxy]phenyl}propanoic acid (657 mg) was obtained as a pale-yellow oil (yield 64%).

^1H NMR ($CDCl_3$) δ: 2.03(3H,s), 2.38(3H,s), 2.63(2H,t,J=7.4Hz), 2.90(2H,t,J=7.4Hz), 4.59(2H,s), 5.00(2H,s), 6.57-7.18(9H,m), 7.23(2H,br s), 7.30-7.44(2H,m).



3-{2-Fluoro-4-[(4'-(4-fluorophenoxymethyl)-2',6'-dimethylbiphenyl-3-yl)methoxy]phenyl}propanoic acid (141 mg) was obtained as colorless prism crystals (yield 14%).

^{1}H NMR ($CDCl_3$) δ: 2.02(6H,s), 2.05-3.00(4H,m), 4.97(2H,s), 5.07(2H,s), 6.62-6.72(2H,m), 6.90-7.14(7H,m), 7.16(2H,s), 7.36-7.50(2H,m).



Formulation Example 1 (production of capsule)

1)	compound of Example 1	30 mg
2)	microcrystalline cellulose	10 mg
3)	lactose	19 mg
4)	magnesium stearate	1 mg
	total	60 mg

The above-mentioned 1), 2), 3) and 4) are mixed and filled in a gelatin capsule.

Formulation Example 2 (production of tablet)

1)	compound of Example 1	30 g
2)	lactose	50 g
3)	corn starch	15 g
4)	carboxymethylcellulose calcium	44 g
5)	magnesium stearate	1 g
	1000 tablets total	140 g

The total amount of the above-mentioned 1), 2) and 3) and 30 g of 4) are kneaded with water, vacuum dried and granulated. The granulated powder is mixed with 14 g of 4) and 1 g of 5) and tableted with a tableting machine. In this way, 1000 tablets containing 30 mg of the compound of Example 1 per tablet are obtained.

Experimental Example 1

Determination of EC_{50} of fatty acid against human GPR40

For determination of EC_{50}, CHO cell line that stably expressed human GPR40 was used. Unless otherwise indicated, the CHO cell line was cultured using α-MEM medium (Invitrogen) containing 10% fetal calf serum (Invitrogen).

The cells cultured to nearly confluent were rinsed with PBS (Invitrogen) on the previous day of the assay, peeled off with 0.05% Trypsin·EDTA solution (Invitrogen) and recovered by centrifugation. The number of the obtained cells was counted, and the cells were diluted such that $3x10^5$ cells were contained per 1 mL of the medium, dispensed to a black welled 96-well plate (coster) by 100 μL per well and cultured overnight in a CO_2 incubator. Various test samples were added to the CHO cells thus prepared, and the changes in the intracellular calcium concentration was measured using FLIPR (Molecular Device). The below-mentioned pre-treatment was applied to measure changes in the intracellular calcium concentration by FLIPR.

An assay buffer for adding a fluorescence dye Fluo3-AM (DOJIN) to the cells, or for washing the cells immediately before FLIPR assay was prepared. To a solution of 1M HEPES (pH 7.4, DOJIN, 20 mL) added to HBSS (Invitrogen, 1000 mL) (hereinafter HBSS/HEPES solution) was added a solution (10 mL) obtained by dissolving probenecid (Sigma, 710 mgi) in 1N NaOH (5 mL), and adding and mixing an HBSS/HEPES solution (5 mL), and the resulting solution was used as an assay buffer. Fluo3-AM (50 μg) was dissolved in DMSO (Wako, 21 μL), and an equivalent amount of 20% pluronic acid (Molecular Probes) was added and

mixed. The solution was added to the assay buffer (10.6 mL) supplemented with fetal calf serum (105 μL) to give a fluorescence dye solution. On the previous day of assay, the medium of the CHO cells newly inoculated to the black welled 96-well plate was removed, the fluorescence dye solution was immediately dispensed by 100 μL per well and the cells were cultured in a CO_2 incubator for 1 hr to allow intake of the fluorescence dye by the cells. The cells after the culture were washed with the above-mentioned assay buffer and set on FLIPR. The test sample was diluted with DMSO in advance, dispensed to polypropylene 96-well plate (sample plate) by 2 μL, and cryopreserved at -20°C. To the thawed sample plate was added an assay buffer containing 0.015% CHAPS (DOJIN) by 198 μL, and simultaneously set on FLIPR together with the cell plate. After the aforementioned pre-treatment, changes in the intracellular calcium concentration upon addition of various test samples was measured by FLIPR. Based on the results, a dose-response curve of each fatty acid was formed and EC_{50} was calculated. The results are shown in Table 1.

【Table 1】

Receptor Function Modulating Action On GPR40	
Compound No.	EC_{50} (μM)
Example 14	0.010
Example 33	0.0061
Example 39	0.032
Example 49	0.011
Example 52	0.049

【Industrial Applicability】

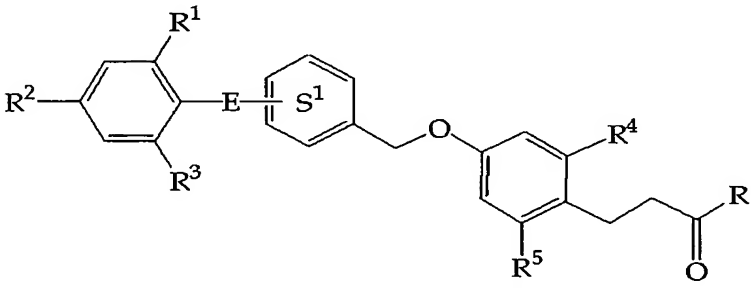
The compound (I), a salt thereof and a prodrug thereof have a superior GPR40 receptor function modulating action and can be used as an agent for the prophylaxis or treatment of diabetes and the like.

【Document】 Abstract

【Summary】

【Problem】 The present invention provides a novel compound having GPR40 receptor function modifying action, which is useful as an insulin secretagogue or an agent for the prophylaxis or treatment of diabetes and the like.

【Solving Means】 The compound represented by the formula (I)



(I)

wherein each symbol is as defined in the specification, a salt thereof and a prodrug thereof having a superior GPR40 receptor function modulating action, which show superior GPR40 receptor agonist activity, and also show superior properties as a pharmaceutical product, such as stability and the like. Thus, they can be safe and useful pharmaceutical agents for the prophylaxis or treatment of GPR40 receptor related diseases in mammals.

【Main Drawing】 None